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AVALIAÇÃO DO CONTROLE ATENCIONAL E EMOCIONAL E DA VARIABILIDADE CARDÍACA EM PACIENTES COM TRANSTORNO DE ANSIEDADE GENERALIZADA

Porto Alegre
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Tese apresentada ao Programa de Pós-graduação em Psiquiatria e Ciência do Comportamento da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de Doutor em Psiquiatria

Orientador: Prof. Dra. Gisele Gus Manfro

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Aprovada em: _____de_____de 2021.

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RESUMO

Considerando a alta prevalência, o curso crônico e a presença de sintomas fisiológicos e cognitivos no TAG, esse estudo buscou explorar os mecanismos cognitivos, emocionais e biológicos do transtorno através de medidas clínicas, biológicas e uma tarefa cognitiva e também apresentar um protocolo de promoção de qualidade de vida para o manejo da ansiedade. Estudos sugerem que o TAG está associado a uma VFC reduzida e é nesse contexto que é desenvolvido o artigo 1. O estudo buscou avaliar se as mudanças da VFC entre as condições de repouso e estresse antes das intervenções poderia predizer melhora na Interferência emocional (IE) em uma tarefa cognitiva após três diferentes tratamentos (fluoxetina, grupo de mindfulness e grupo controle de qualidade de vida) para o TAG. Nesse artigo discute-se a necessidade de marcadores clínicos, psicológicos e biológicos acessíveis para o desenvolvimento de intervenções eficazes e personalizadas para o tratamento do TAG. Sabe-se também que a ansiedade e a preocupação estão associadas a déficits no processamento cognitivo e emocional. Diante disto, no artigo 2 avaliamos a associação entre o controle atencional e a interferência emocional em pacientes com TAG e seus efeitos nas diferentes modalidades de tratamento. Os dados apontam que as três intervenções melhoram o desempenho cognitivo e podem modificar o processamento cognitivo, emocional e reações comportamentais frente a estímulos emocionais de maneiras diferentes.

Desenhando possibilidades de tratamento para o TAG, o artigo 3 apresentada um protocolo de tratamento em grupo baseado em psicoeducação e qualidade de vida para pacientes com o TAG que apresentou melhora significativa da qualidade de vida em todos participantes e que pode ser aplicado por profissionais da saúde não especialistas na área da psicologia e psiquiatria. Diante do impacto do TAG na saúde global e a dificuldade em estabelecer tratamentos eficazes, os dados apontam que as três intervenções podem atuar nos mecanismos emocionais, cognitivos e fisiológicos da ansiedade por meio de diferentes mecanismos. Sendo assim, o presente estudo fornece dados de como futuras pesquisas podem ser projetadas em direção a neurociência e tratamentos psicossociais personalizados para os transtornos de ansiedade.

Palavras-chave: transtorno de ansiedade generalizada; controle atencional; interferência emocional; variabilidade cardíaca; qualidade de vida.

ABSTRACT

Considering the high prevalence, the chronic progression, the presence of physiological and cognitive symptoms in GAD, this study sought to explore the cognitive, emotional, and biological mechanisms of the disorder through clinical and biological measures and a cognitive task, and also to present a life quality-promotion protocol for managing anxiety. Studies suggest that GAD is associated with a reduced cardiac HRV, and it is within this context that article one was developed. The study sought to assess whether changes in HRV between rest and stress conditions before interventions could predict improvements in GAD Emotional interference (EI) in a cognitive task after three different treatments (fluoxetine, mindfulness group, and quality of life control group). This article discusses the need for accessible clinical, psychological, and biological markers for the development of effective and personalized interventions for the treatment of GAD. It is also known that anxiety and worry are associated with deficits in cognitive and emotional processing. Given this, article two sought to assess the association between attentional control and emotional interference in patients with GAD and its effects in different treatment modalities. The data indicate that the three interventions improve cognitive performance and can modify cognitive and emotional processing and behavioral reactions to emotional stimuli in different ways.

Outlining treatment possibilities for GAD, article three presents a group treatment protocol based on psychoeducation and quality of life promotion for patients with GAD that showed a significant improvement in the quality of life in all participants and that can be applied by health professionals who are not specialists in the field of psychology and psychiatry. Given the impact of GAD on global health and the difficulty in establishing effective treatments, the data indicate that the three interventions can act on the emotional, cognitive, and physiological mechanisms of anxiety through different mechanisms. Therefore, the present study provides data on how future research can be designed towards neuroscience and personalized psychosocial treatments for anxiety disorders.

Keywords: generalized anxiety disorder, attention control, emotional interference, heart variability, quality of life

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LISTA DE ABREVIATURAS E SIGLAS

APA	American Psychiatric Association
BMT	Body in Mind Training
CCA	Córtex Cingulado Anterior
CCAd	Córtex Cingulado Anterior Dorsal
CPFm	Córtex Pré-Frontal Medial
CPFdm	Córtex Pré-Frontal Dorsomedial
CPFvm	Córtex Pré-Frontal Ventro-Medial
CPF	Córtex Pré-Frontal
CRH	Hormônio Liberador De Corticotrofina
CPFdb	Córtex Pré-Frontal Dorsomedial Bilateral
DERS	Difficults in Emotion Regulation Scale
DSM	Manual Diagnóstico e Estatístico de Transtorno Mentais, 5a Edição
FC	Frequência Cardíaca
GABA	Ácido Gama-Aminobutírico
HAMA-A	Hamilton Anxiety Rating Scale
HAMA-D	Hamilton Rating Scale for Depression
IAPS	International Affetive Picture System
IBI	Intervalos Inter-Batimentos
IRSN	Inibidores de Receptação de Serotonina e Norepinefrina
ISRS	Inibidores de Receptação de Serotonina
MINI	Mini-International Neuropsychiatric Interview
MBSR	Redução de Estresse Baseada em Mindfulness
PSQW	Penn State Worry Questionnaire
RA	Relaxamento Aplicado
SNA	Sistema Nervoso Autônomo
TAG	Transtorno de Ansiedade Generalizada
TCC	Terapia Cognitivo-Comportamental
VFC	Variabilidade da Frequência Cardíaca

SUMÁRIO

1 APRESENTAÇÃO

Este trabalho consiste na tese de doutorado intitulada “Avaliação do controle atencional e emocional e variabilidade cardíaca em pacientes com transtorno de ansiedade generalizada” que buscou explorar os mecanismos emocionais, cognitivos e fisiológicos da ansiedade. O trabalho foi desenhado e realizado dentro do grupo de pesquisa em ansiedade da UFRGS e apresentado dentro do Programa de Pós-Graduação de Ciências do Comportamento e Psiquiatria da Universidade Federal do Rio Grande do Sul em julho de 2021. O trabalho é apresentado em parte, na ordem que segue:

- Introdução
- Revisão da literatura
- Objetivos
- Artigos
- Conclusões

2 INTRODUÇÃO

A ansiedade e o medo são emoções naturais e básicas necessárias para a sobrevivência do indivíduo mas também são emoções desconfortáveis e aversivas (1). Na ansiedade, o estímulo que dispara a reação ansiosa pode ser interno, menos específico e de forma antecipatória (2). Quando essa emoção esta presente de maneira exagerada ou disfuncional, no nível cognitivo, afetivo, comportamental ou fisiológico, ela pode ser considerada como um transtorno mental (3–5).

Os transtornos de ansiedade são uma das apresentações disfuncionais dessa emoção, sendo caracterizados por um patógeno complexo – interação entre fatores ambientais e múltiplos variantes genéticos. A herdabilidade de transtornos de ansiedade, ou seja, a participação de fatores genéticos no seu desenvolvimento, situa-se na faixa de 30 a 67%, com o restante contabilizado com fatores individuais negativos. Em contrapartida, fatores ambientais positivos como estilos de apego seguro, estratégias de enfrentamento e rede de apoio, mesmo na presença de fatores de risco genéticos, podem aumentar a resiliência, desenvolvimento de recursos emocionais e se opondo ao desenvolvimento de um transtorno de ansiedade (6).

O Transtorno de Ansiedade Generalizada (TAG) faz parte dos transtornos de ansiedade e é classificado, pelos manuais diagnósticos, pela presença constante e recorrente de preocupações que são difíceis de controlar e que ocorrem na maior parte do dia por pelo menos seis meses (7). O conteúdo das preocupações deve ser relacionado a diversos eventos ou atividades, como: desempenho acadêmico ou profissional, família, relacionamentos, doenças e finanças, não se restringindo a temas característicos de outros transtornos psiquiátricos. No atual Manual diagnóstico e estatístico dos transtornos mentais da Associação Psiquiátrica Americana (7), o critério para o TAG somente é preenchido se três ou mais dos seguintes sintomas também estiverem presentes: inquietação ou sensação de estar com os nervos à flor da pele, fadiga aumentada, dificuldades de concentração ou falha de memória, irritabilidade, tensão muscular e problemas de sono (7). Ainda existe a intolerância à incerteza refletida na dificuldade em tomar decisões e a frequente presença de desconfortos físicos crônicos como: distúrbios gastrointestinais, dores de cabeça, fadiga, entre outros, que não têm explicação médica. Os sintomas físicos derivam dos níveis cronicamente elevados dos hormônios do estresse liberados por excessiva preocupação (8–10).

Em relação ao prognóstico, estudos apontam o TAG como o transtorno de ansiedade com o curso mais crônico, com maior incidência de comorbidades psiquiátricas (11) e com pior

resposta ao tratamento psicoterápico e farmacológico (12). Estudos epidemiológicos recentes indicam uma prevalência do transtorno ao longo da vida em torno de 3,1% (13) e 3,7% (14) na população geral com taxa de comorbidade de 81,9%, sendo destes 63% com transtornos de humor e 51% com outro transtorno de ansiedade (15).

Em termos de custos para a sociedade, o TAG é considerado um dos transtornos mentais mais impactantes em relação ao uso do sistema de saúde bem como um prejuízo funcional no ambiente de trabalho. Indivíduos acometidos pela doença são os usuários mais comuns na rede básica de saúde e ambulatórios de especialidades, adicionando consideravelmente os custos não psiquiátricos relacionados as dificuldades médicas nos transtornos de ansiedade (16–18). Dados apontam para uma prevalência de aproximadamente 10% dos pacientes com TAG acometidos por doença cardiovascular em países ocidentais (19), 15% a 23% de indivíduos com TAG diagnosticados ou recebendo tratamento para câncer com sintomas atingindo até 69-79% em níveis mais avançados da doença (20,21) e 32% a 57% da presença do transtorno em pacientes com doenças respiratórias indicando alta prevalência de adultos com ansiedade e doença pulmonar obstrutiva crônica (22).

O Modelo teórico do TAG apresenta a preocupação excessiva como uma estratégia persistente e ineficaz para lidar com a ansiedade e emoções desagradáveis perpetuando o transtorno e mantendo os déficits em regulação emocional (23). Os achados demonstram que pessoas com TAG apresentam intensidade emocional aumentada e uma reatividade negativa às próprias emoções comparado a outras populações clínicas (23). Indivíduos com TAG utilizam a preocupação como forma de atenuar o impacto emocional de estímulos aversivos repentinos e/ou imagens mentais (24,25). Acredita-se que as preocupações tenham o papel de evitação. Elas são mantidas pela eliminação, atenuação ou adiamento de uma estimulação aversiva (o reforço negativo) (26) ou seja, elas são utilizadas como um controle emocional para reduzir emoções negativas.

Uma série de mecanismos neurofisiológicos foram identificados como geradores e influenciadores de respostas ao medo e à ansiedade em possíveis sinais de perigo. Algumas estruturas estão envolvidas nestas respostas; o tálamo integra a entrada sensória para o córtex sendo responsável em posteriormente enviar as informações para a amigdala (27,28). A amigdala e o córtex cingulado anterior dorsal (CCAd) processam sinais aversivos enviando essas mensagens ao hipotálamo, gânglios basais e tronco cerebral para impulsionar comportamentos defensivos. Assim, o hipocampo opera na identificação de informações no ambiente associadas a sinais de ameaças, enquanto o córtex pré-frontal medial (CPFm) é responsável pelo controle regulatório top down da resposta do medo, recebendo informações

do hipocampo e tálamo, enviando essas para a amigdala, modulando então a resposta ao medo (29–31) Corroborando estas evidências dos mecanismos neurofisiológicos envolvidos na ansiedade, achados baseados em estudos de neuroimagem estrutural e funcional apontam para diferenças entre pacientes com TAG e indivíduos controles concentrando-se no córtex cingulado anterior (CCA) e na amigdala (32–34).

Outro mecanismo fisiológico afetado no TAG é a variabilidade da frequência cardíaca (VFC), compreende a flutuação no ritmo da frequência cardíaca (FC) e é resultado de interações complexas entre diferentes sistemas, como sistema nervoso autônomo, mecanorreceptores, regiões do sistema nervoso central (como amígdala, córtex insular e pré-frontal), medula espinhal, e também um sistema nervoso intrínseco do coração. Um nível adequado de variabilidade no ritmo cardíaco durante o repouso revela a capacidade regulatória de um organismo de se adaptar a diferentes condições (35,36). O oposto é verdadeiro. Sabe-se, por exemplo, que a VFC reduzida é preditiva de todas as causas de mortalidade (37). Condições psiquiátricas como ansiedade (38,39) depressão (40) e transtorno de estresse pós-traumático (39,41) também estão associados a uma VFC diminuída. Especificamente, estudos com TAG e seu principal sintoma (preocupação) sugerem que o TAG está associado a VFC reduzida (39,42,43).

Estudos recentes sobre conectividade entre as regiões cerebrais em pacientes ansiosos indicam uma diminuição da conectividade entre as regiões do processamento emocional (amigdala e ínsula) e da modulação emocional. Análises funcionais apontam uma diminuição da conectividade entre a amigdala e o CPFm no TAG (44,45). Diferenças da conectividade são evidenciadas em pacientes ansiosos em relação aos controles na diminuição da conectividade entre a amigdala e a ínsula no TAG (46–48). Ao que parece, os transtornos de ansiedade envolvem déficits de conexão nas regiões geradoras de emoção e regiões regulatórias, sugerindo que tanto ansiedade como o medo, desempenham funções essenciais no complexo espectro da ansiedade.

Recentemente, estudos de neuroimagem estrutural identificaram alterações em pacientes com TAG comparados aos controles. Foram encontrados aumento volumétrico de substância cinzenta na amigdala e no córtex pré-frontal dorsomedial (CPFdm) assim como uma diminuição do volume do hipocampo (49,50). Estudo com adolescentes com TAG demonstraram aumento no giro temporal superior e diminuição nos giros mediais e superiores frontais (44). Outros estudos que analisaram a conectividade estrutural em pacientes com TAG também investigaram a amigdala e demonstraram a diminuição da amigdala e o córtex cingulado anterior (CCA) e o córtex pré-frontal (CPF) em comparação aos indivíduos controle

(51,52). Outros dados interessantes descreveram o aumento do volume de substância cinzenta no CPFdm e aumento da densidade neuronal no CPFdm direito em adultos (53), mas não em crianças ou idosos (46,50).

A presença de um viés no processamento de informações relativas a ameaça está relacionada a etiologia e manutenção dos transtornos de ansiedade (54,55). O modelo de Barlow (2000) (56), descreve uma vulnerabilidade biológica e psicológica aos elementos negativos da vida nos transtornos de ansiedade. Focar a atenção em possíveis sinais de ameaça promove essa vulnerabilidade e a percepção de uma incapacidade de controlar os eventos da vida. A Teoria do controle da atenção é uma abordagem que relaciona a ansiedade e cognição e que contribuiu para o desenvolvimento da Teoria de eficácia do processamento (55). A ansiedade aumenta a excitação e facilita o processamento sensorial bottom-up (57), contudo, pode interromper o controle cognitivo top-down causado por interferência interna e externa (58,59). Acredita-se que indivíduos ansiosos usualmente alocam recursos da atenção para estímulos relacionados a ameaças internas (pensamentos ruminativos, preocupações) ou externos (distratores irrelevantes para a tarefa). Desta forma, altos níveis de preocupação estão associados a baixos níveis de desempenho (60).

Por um lado, as tarefas de atenção parecem ser essencialmente vulneráveis a lapsos de atenção, incluindo interrupção e erros devido a cognição ansiosa (58,61,62). De outro lado, embora possa interferir na cognição e interferir no desempenho, a ansiedade pode facilitar o processamento de informações e respostas comportamentais. Estudos prévios, confirmam que a ansiedade pode aumentar o controle inibitório de respostas prepotentes – um mecanismo que é adaptativo sob ameaças- reduzindo significativamente erros ao longo dos testes (63,64). Assim, as tarefas de atenção/vigilância poderiam se beneficiar das propriedades estimulantes da ansiedade (59). Em metanálise, incluindo 172 estudos comparativos entre pessoas ansiosas e não ansiosas, verificou-se que independente do transtorno de ansiedade, pessoas ansiosas apresentam um viés atencional voltado para ameaça significativamente maior que os não-ansiosos (65)

O tratamento para o TAG inclui a diminuição dos sintomas de ansiedade, redução do prejuízo da funcionalidade e melhora da qualidade de vida (66,67). Ao longo da história, os transtornos de ansiedade foram tratados inicialmente com medicações que tinham efeitos sedativos, incluindo álcool, opiáceos, beta-bloqueadores e essencialmente os benzodiazepínicos (68). Atualmente, os antidepressivos substituíram os benzodiazepínicos como o tratamento farmacológico de primeira escolha para o TAG principalmente por não terem as propriedades aditivas dos benzodiazepínicos (69–72). Dentre os antidepressivos, os inibidores de recaptação

de serotonina (ISRS) e inibidores de recaptação de serotonina e noradrenalina (IRSN) são considerados padrão ouro para o tratamento do transtorno porém com taxas de resposta de 30 a 50% (71,73). A eficácia dos antidepressivos tricíclicos é similar ao ISRS (73), mas este grupo de fármacos tem um perfil de tolerabilidade e segurança menos favorável. Os benzodiazepínicos são eficazes no tratamento do TAG (70), contudo, devido ao risco de abuso e dependência não são usualmente considerados para o tratamento em monoterapia. Estudos com o uso de benzodiazepínicos em indivíduos com TAG, verificou-se um prejuízo cognitivo e da função motora e potencial de dependência fisiológica com o uso crônico (71,74).

A primeira intervenção não farmacológica que se descobriu eficaz no tratamento do TAG foi o relaxamento aplicado (RA) (75), que é até hoje considerado tratamento de primeira linha no transtorno. A partir dos primeiros anos da década de 1990, protocolos de Terapia Cognitivo-Comportamental (TCC) usando técnicas de psicoeducação, reestruturação cognitiva e exposição, passaram a ser sistematicamente testados e obtiveram a mesma eficácia que o RA (75). Posteriormente, a TCC passou a ser considerada a terapia padrão-ouro para o TAG (17,76). Revisão sistemática avaliou uma amostra representativa de 106 estudos examinando a TCC para os principais transtornos psiquiátricos. Onze estudos compararam a TCC a outro tratamento ou grupo controle e encontraram taxas de respostas mais altas na TCC em 7 destes estudos e apenas uma apresentou taxas mais baixas na TCC frente aos grupos de comparação (77). Recente meta-análise apontou quatorze ensaios clínicos randomizados avaliando a eficácia da TCC em comparação a outro tratamento ou grupo controle para o TAG, com um total de 772 participantes, encontrou um tamanho de efeito médio do grupo de tratamento em TCC em comparação com qualquer controle (g=0,66) (78).

Outra possibilidade de intervenção terapêutica é o treinamento em atenção plena-Mindfulness – que trata o TAG por meio de ajustes em processos e padrões cognitivos. As práticas de Mindfulness tem a intenção de desenvolver a capacidade de observar a experiência sem julgá-la ou reagir a ela. Vai sendo desenvolvida em etapas, sendo a primeira a capacidade de sustentar a atenção, notando os devaneios e desenvolvendo a habilidade de se desengajar dos pensamentos e retornar ao estímulo sensorial escolhido, seja o corpo inteiro (através do escaneamento corporal), seja a respiração, sejam as sensações evocadas por movimentos (como a caminhada meditativa). A segunda etapa envolve a habilidade de ampliar o foco para uma visão ampla, ou seja, assistir há entrada dos estímulos sem reagir a eles, percebendo sua mudança e desvanecimento, e a entrada dos estímulos subsequentes. A terceira etapa envolve o desenvolvimento de emoções positivas, como a compaixão e a bondade amorosa, para si e para os demais indivíduos (79,80). Pesquisas têm evidenciado as abordagens de atenção plena

como possibilidade terapêutica eficaz em indivíduos com TAG (81–83). Os resultados apontam melhora significativa na ansiedade, preocupação e depressão no pós tratamento e os benefícios se mantêm em acompanhamentos de três a seis meses (84–86). Redirecionar a mente para o presente momento gera pensamentos mais funcionais e processos mais saudáveis, tornando o treinamento em atenção pela um tratamento eficaz a longo prazo para o TAG (87).

A alta prevalência e o nível de prejuízo e sofrimento dos indivíduos acometidos pelo TAG justifica o investimento em pesquisas clínicas que investiguem os mecanismos cognitivos, emocionais e biológicos envolvidos no transtorno a partir de diferentes intervenções clínicas. A partir do presente estudo, buscou-se um entendimento sobre a gênese e manutenção do transtorno a partir de variáveis cognitivas, emocionais e biológicas, o que poderá ser utilizado para um delineamento quanto as melhores estratégias e intervenções terapêuticas para pacientes com TAG.

3 REVISÃO DA LITERATURA

3.1 Ansiedade

A ansiedade é uma emoção que acompanha o homem desde a sua existência, visto que possui um caráter adaptativo e protetivo e pode ser considerada um sinal de alerta frente a uma ameaça ou perigo existente. Enquanto a ansiedade patológica, se diferencia pela intensidade, duração e desproporcionalidade frente a uma ameaça percebida e não real (88). A ansiedade e o medo fazem parte da natureza humana e se inserem em um sistema complexo que objetiva, principalmente, assegurar a sobrevivência da estrutura biológica. O medo pode ser entendido como uma resposta neurofisiológica acionada a partir da identificação cognitiva ou uma sensopercepção de uma situação de ameaça, enquanto a ansiedade pode ser entendida como um sistema de maior complexidade acionado pelo medo. Tecnicamente, o medo se distingue da ansiedade pela presença de um estímulo claro e delimitado que produz tal emoção (89,90).

A ansiedade é adaptável, prepara o organismo para a ação, aumenta a excitação, ativa o processo bottom-up de atenção e também pode interferir no processo top-down ocasionado por interferências internas e externas em tarefas de estímulos distratores (58,61). Evidências sugerem que a ansiedade pode estar envolvida em um déficit no controle de atenção no processamento de estímulos relevantes para a tarefa quando distratores estão presentes. Indivíduos ansiosos demonstram baixo recrutamento das regiões corticais frontais implicadas no controle atencional (91). A ansiedade é entendida como um estado motivacional e emocional aversivo que acontece pela antecipação de situações ameaçadoras. Skinner (1937) (92), define a ansiedade como uma condição emocional complexa e aversiva que é condicionada através de um emparelhamento de estímulos neutros para negativos. A teoria do condicionamento sugere que estímulos que antes não eliciavam respostas de ansiedade, a partir de determinada situação, passam a ser sentidos de forma aversiva e respondidos com comportamentos de luta e/ou fuga e evitação (93). Quando alguma situação de perigo é percebida ou interpretada, o cérebro envia um sinal de alerta ao sistema nervoso central, responsável por transmitir todas as informações para o nosso organismo, e ele então que prepara o corpo para a resposta frente aos estímulos. Enquanto o sistema nervoso simpático libera energia e prepara o corpo para a ação, o parassimpático é o sistema de restauração, que prepara o organismo para voltar ao seu estado normal. Assim, o estímulo ameaçador é captado pelo sistema nervoso simpático, que aciona os mecanismos de luta e fuga frente a estímulos reais ou percebidos de perigo.

A experiência subjetiva de medo e ansiedade pode se desenvolver de forma crônica, como no transtorno de ansiedade generalizada, em que o indivíduo manifesta de forma contínua, quase todos os dias, preocupações acerca de diversos domínios, causando grande sofrimento.

3.2 Transtorno de Ansiedade Generalizada (TAG)

3.2.1 Conceito e caracterização

Os transtornos de ansiedade são os transtornos psiquiátricos mais prevalentes com uma prevalência mundial em torno de 7.3% (94). Aproximadamente, 11,6% dos indivíduos em todo mundo são diagnosticados com um transtorno de ansiedade em um ano (66,95) e, ao contrário de outros transtornos psiquiátricos, os transtornos de ansiedade afetam os indivíduos de forma mais precoce, reduzindo os anos de produtividade (12). O Transtorno de Ansiedade Generalizada (TAG) é caracterizado por ansiedade e preocupação persistentes e excessivos com relação às questões do cotidiano, que são difíceis de controlar e que duram por, pelos menos, 6 meses (7,96). Os indivíduos podem experienciar sintomas físicos como inquietação ou se sentirem "no limite", ficar facilmente fatigados, ter dificuldades de concentração ou ter "brancos", irritabilidade, tensão muscular e alteração do sono (7). O TAG é um dos transtornos mentais mais comuns no cuidado primário e está associado ao aumento do uso de recursos de saúde e à incapacidade (97). A prevalência é de 3,1% em 12 meses e ao longo da vida é de aproximadamente 6% (13). O TAG ocorre duas vezes mais em mulheres e está associado com ter mais do que 24 anos, ser solteiro, divorciado, viúvo ou não ter emprego (97,98). O pico de prevalência se dá na meia idade e declina ao longo dos anos sendo a média de idade de início do transtorno aos 30 anos (13,94). Os sintomas tendem a ser crônicos; o curso flutuante, e a taxa de remissão completa é extremamente baixa (7).

Este transtorno está associado a prejuízo funcional, comorbidades médicas e psiquiátricas (97,99,100). As comorbidades psiquiátricas são frequentes, sendo que aproximadamente 66% dos indivíduos com TAG têm, pelo menos, outro transtorno psiquiátrico, especialmente depressão ou outro transtorno de ansiedade (101). Em mulheres, a principal comorbidade é a depressão, enquanto que o Transtorno por uso de substância é a mais importante nos homens (7). Indivíduos com o transtorno apresentam um risco maior de ideação suicida e tentativas de suicídio comparados com indivíduos sem transtornos de ansiedade (102). O TAG também está associado a comorbidades clínicas e parece prever, independentemente, o

aumento do risco para doença cardíaca coronariana na população em geral (103). Também, o TAG está associado com síndromes dolorosas (104), doença cardíaca (100,105) e doenças do trato gastrointestinal (Comer et al., 2011). Apesar da sua prevalência e do seu prejuízo, o TAG ainda é um transtorno subdiagnosticado e menos de um terço dos pacientes são adequadamente tratados (106,107).

Entre todos os processos e mecanismos envolvidos no TAG, a preocupação tem sido amplamente estudada e entendida como ponto central na patogênese do transtorno (3,108). A preocupação está relacionada a uma emocionalidade negativa e ativação fisiológica com aumento da ativação do sistema nervoso simpático, aumento da atividade cardiovascular, diminuição do sistema nervoso parassimpático e redução variabilidade da frequência cardíaca (36). Segundo alguns estudos, ao medir os níveis absolutos de emocionalidade entre tarefas, a preocupação gerou um aumento da emocionalidade negativa em relação a linha de base (em comparação a estados de relaxamento e tarefas neutras) que permaneceu ativa durante a exposição a imagens negativas (93,109).

Acredita-se que a preocupação tem uma função evitativa, atuando como um recurso cognitivo de defesa. O papel da preocupação na ansiedade foi descrito inicialmente por Borkovec e Costello, (1993) (75), e que, anos mais tarde, consolidou a "teoria da preocupação evitativa". Estudos recentes referentes a conceituações de preocupação, afirmam que o aumento da previsibilidade da experiência emocional negativa, reforça o caráter tranquilizador da evitação. Conjuntamente, processos associados como a intolerância à incerteza, não aceitação emocional e desregulação emocional aumentam a preocupação (110–112). O modelo cognitivo do TAG afirma que a preocupação patológica presente no transtorno é resultante de crenças negativas sobre estratégias preocupantes e contraproducentes de controle mental. A maioria dos indivíduos com o transtorno desenvolvem crenças positivas sobre a preocupação, "A preocupação me mantém seguro", " A preocupação me ajuda a enfrentar", " Se eu me preocupar com danos no futuro, serei capaz de evitá-los", o que reforça a ideia da preocupação como algo produtivo e necessário. Ainda assim, sabe-se que a preocupação excessiva ou inflexibilidade em lidar com pensamentos negativos pode ocasionar em dificuldades de regulação emocional (113,114).

A ruminação e a preocupação são processos cognitivos intimamente relacionados e que estão presentes em indivíduos com TAG (115). Contudo, sabe-se que existem diferenças nas funções destes estilos de pensamentos para a manutenção do transtorno. A preocupação está associada a uma antecipação de futuro que tenta reduzir ou minimizar a possibilidade de problemas futuros e que pode atuar como uma estratégia de evitação de emoções negativas

frente a pensamentos catastróficos de situações que podem vir a ocorrer. Enquanto, a ruminação, ocorre através de pensamentos voltados a causas e consequências de problemas do passado, sem uma atitude ativa de resolução de problemas (52,116). Pesquisadores postulam que a relação entre a preocupação e evitação é estabelecida a partir das crenças de indivíduos com TAG sobre as suas experiências e preocupações. Acredita-se que sujeitos excessivamente preocupados, com ou sem TAG, monitoram e pensam mais sobre os seus próprios pensamentos (metacognição; pensar sobre o pensar) e acreditam que se preocupar é uma estratégia funcional (117)

A Teoria da eficiência do processamento defende o entendimento da preocupação como componente da ansiedade e responsável pelos efeitos da ansiedade na eficácia e eficiência de desempenho. Assume-se que a preocupação atua no desempenho cognitivo através da redução da atenção e da capacidade de armazenamento temporário da memória de trabalho, que estão, desta forma, menos disponíveis para tarefas simultâneas em processamento (60,118). Os efeitos da preocupação e, por consequência, da ansiedade estão associadas às funções executivas. Desta forma, os efeitos da ansiedade sobre o desempenho são maiores em atividades que exigem um processamento e armazenamento da memória de trabalho.

3.2.2 Etiologia

Fatores genéticos, neurofisiológicos e temperamentais individuais vão gerar uma vulnerabilidade cognitiva que predispõem o indivíduo a aumentar ou diminuir a resposta ansiosa frente a alguma situação ou agente estressor. Nos últimos anos, pesquisas apontaram que a vulnerabilidade biológica é um alto preditor para o desenvolvimento dos transtornos de ansiedade, onde a hereditariedade varia de 30 a 40%. Uma meta-análise realizada com gêmeos estimou a herdabilidade no TAG em 32% (119), embora, estimativas mais altas de 49% e sem diferença de sexos, foram observadas em um estudo transversal com gêmeos na Suécia (120). A vulnerabilidade genética é percebida através de elevações nos traços gerais da nossa personalidade ou do temperamento ou do traço de ansiedade. Pessoas com genitores ou avós com transtornos de ansiedade têm mais chances de desenvolver a doença. Algumas estruturas neuroanatômicas associadas (amígdala, lócus coeruleus, córtex pré-frontal direito) e diferenças nos transmissores de serotonina, ácido gama-aminobutírico (GABA) e hormônio liberador de corticotrofina (CRH) são algumas outras vulnerabilidades biológicas na ansiedade que interagem com a vulnerabilidade cognitiva (49,53,119,121).

3.3 Processos cognitivos

3.3.1 Controle atencional

A adaptação em um ambiente complexo e com diversas possibilidades de estímulos, exige a capacidade de permanecer orientado para uma tarefa contínua, apesar da entrada de novos estímulos salientes distratores. Modelos atuais sugerem que os fatores bottom up e top-down influenciam diretamente a alocação de atenção (118). Durante os processos atencionais, mecanismos pró-ativos de atenção, caracterizados de cima para baixo, chamados de "top-down", com critério de seleção de variáveis, selecionam a entrada de estímulos, com base em expectativas, objetivos e conhecimentos, são utilizados para manter a atenção em tarefas contínuas. Os processos denominados de "bottom-up" possibilitam a entrada de novidades ou destaques, como estímulos emocionais. A interação entre esses mecanismos foi investigada com diferentes métodos e populações (122–124). Estudos com imagens de rostos com expressões de raiva são detectados mais rapidamente que rostos neutros (112,118), assim como rostos ameaçadores são processados antes em comparação com outras expressões faciais (64). Encontrou-se tempos de reação mais rápidos na detecção de palavras negativas comparadas a palavras neutras (91).

A percepção de ameaças inicia antes de um encontro com o estímulo, acredita-se na ideia de vieses atencionais pré-estímulos que afetam a percepção de sinais de ameaças e que tal processo é influenciado pelos fatores top-down e bottom-up (125). Tais comportamentos são vistos em nosso dia-a-dia através da busca antecipatória, com o objetivo de detectar rapidamente fontes de recompensa ou ameaça em potencial. Vieses do pré-estímulo podem ser particularmente importantes na ansiedade, uma vez que a ansiedade está associada a hipervigilancia de perigos e uma superestimativa da probabilidade de eventos negativos futuros (112,126).

Os efeitos bottom-up, como a detecção de ameaças por exemplo, estão possivelmente relacionados a respostas em várias regiões cerebrais que estão em maturação precoce como a amigdala, cingulado anterior e córtex orbitofrontal. Fatores top-down, memória de trabalho, seleção de respostas e mudanças de esforço de atenção, são provavelmente mediados por regiões do cérebro córtex pré-frontal, lateral e parietal posterior que ainda não atingiram a maturidade funcional (59,65). Estudo examinou a associação entre ansiedade, idade e alocação de atenção e resposta fisiológica às ameaças e demonstrou que as relações entre atenção e excitação autônoma apontam para uma interação complexa entre os fatores bottom-up e top-

down (124). Desta forma, em adultos maduros com ansiedade, isso pode ocasionar em um objetivo organizado de evitar experiências negativas, enquanto em crianças essa função não está madura o suficiente para influenciar o controle atencional (127).

Uma das funções principais do sistema de controle executivo deve ser filtrar ou inibir os estímulos irrelevantes, que são, por vezes, estímulos emocionais que interferem na tarefa principal. Além disso, o sistema executivo opera com a memória de trabalho, um sistema que regula a manutenção das informações disponíveis (128). Assume-se que distratores emocionais poderão interferir e comprometer o desempenho em tarefas atencionais (129). Os resultados de um estudo com pacientes ansiosos mostraram uma desaceleração do ritmo de resposta após a apresentação de um estímulo emocional aversivo (130). Em contrapartida, estudo prévio com a tarefa Stroop não encontrou efeitos significativos da valência de distratores emocionais no desempenho cognitivo (118). Da mesma forma, uma série de estudos, utilizando a tarefa Flaker, verificaram que os participantes eram imunes a interferência dos distratores emocionais. Tais achados são apoiados no entendimento de que os estímulos incongruentes possam envolver processos executivos que auxiliam os participantes a filtrar os estímulos distratores emocionais (129,131). Ainda assim, a variabilidade entre estudos de distração com a tarefa Stroop decorre para além das diferenças processuais e sim da influência de características individuais e possíveis traços de ansiedades dos participantes (131,132). Diversos estudos têm apontado para o papel da ansiedade e o seu viés seletivo de atenção para uma perspectiva negativa frente aos estímulos apresentados, enviesando o sistema atencional para o processamento bottom-up (58,118).

A relação entre ansiedade e cognição têm sido estudada extensivamente por estudiosos da área (58,133,134). Alguns destes estudos, apontam que o aumento da carga da memória de trabalho diminui a ansiedade, o que pode facilitar o desempenho cognitivo em situações estressantes, deslocando a atenção para a tarefa presente e afastando-se de pensamentos preocupantes e ruminativos (134–136).

Informações emocionais direcionam para possíveis mudanças no ambiente e podem ser utilizadas para guiar os comportamentos dos indivíduos. Desta forma, uma redução na regulação das respostas emocionais está associado a baixa capacidade de adaptação as demandas da vida, bem-estar psicológico, índices de afetivo negativo e ansiedade (137–139).

Estudos com tarefas cognitivas e imagens emocionais indicam que estímulos emocionais inibem as respostas quando comparados a estímulos neutros, comprovando que o desempenho em tarefas cognitivas é mediado pela percepção e processamento de estímulos emocionais (140–142). Autores revelaram que a apresentação de imagens emocionais intensas

provoca lentificação, caracterizado pela parada de respostas corretas frente a tarefa cognitiva (143). Em testes com imagens de valência emocional negativas, como Go/no Go, os participantes apresentam maiores erros nas respostas (144). Um estudo investigou a relação entre os processos cognitivos e a inibição de respostas motoras através da apresentação de estímulos emocionais e medição da VFC. Os achados deste estudo evidenciaram que, após a apresentação de imagens de valência emocional negativa, os participantes precisavam de mais tempo para iniciar e parar a resposta planejada comparado com a apresentação de imagens neutras (35).

O processamento visual é aprimorado para estímulos relevantes. Sabe-se que visualizar imagens de conteúdo emocional aversivo (corpos mutilados, nus, lesões corporais) produz um conjunto de efeitos cognitivos e comportamentais que promovem respostas com um viés emocional (145). A partir disso, uma sequência de modulação emocional, ativação autonômica e comportamento (147) defensivo são apresentadas pelo indivíduo (146,147). Em tarefas comportamentais, a apresentação de estímulos emocionais gerou respostas mais rápidas em paradigmas de figuras de animais como aranhas e cobras versus estímulos neutros, (136) em rostos com emoção de raiva (brabos) e de medo (assustados), com figuras neutras ou felizes (148,149) e em cenários desagradáveis versus cenários neutros ou agradáveis (150). Um estudo examinou a modulação do controle da atenção no processamento de emoções utilizando expressões corporais e faciais. Os resultados sugerem que a valência emocional de um estímulo corporal pode ultrapassar os mecanismos de filtragem de atenção, ou seja, os estímulos distratores emocionais levam a atenção a se desviar da tarefa principal (151). Em uma série de experimentos sobre estímulos agradáveis e desagradáveis, revelou-se que os processos cognitivos no nível de seleção de resposta, são facilitados pelo conteúdo da cena e atrasados pela presença de pistas aversivas intrusivas. Observou-se que estímulos desagradáveis produziam desaceleração das respostas, enquanto estímulos agradáveis aceleração das respostas. Ainda assim, tais achados não concluem se os efeitos do tempo de resposta são em detrimento do envolvimento emocional do observador ou como resultado da orientação da atenção inicial voltada para estímulos agradáveis em comparação com os desagradáveis (152). Estudo realizado por Grillon et al (2016) (153) avaliou fatores que podem influenciar na melhoria de desempenho através da apresentação de um teste de vigilância que sonda a inibição de respostas a estímulos com sessenta indivíduos saudáveis. Confirmou-se a hipótese de que a ansiedade aumenta o controle inibitório de respostas prepotentes e este efeito é maior naqueles que dependem mais de tais respostas, ou seja, indivíduos com baixo controle atencional.

O controle atencional é considerado um dos mecanismos de regulação emocional. Estima-se que, tanto a orientação, como a atenção seletiva, influenciam o processamento de estímulos desde um estágio precoce até a regulação emocional (154). Uma das premissas centrais da meditação é o treino de atenção focada, entendido como uma habilidade de sustentar um foco internalizado que auxilia no controle das distrações internas ou externas (podendo ser emocionais ou de outra ordem) (155) . Com base neste treino, o controle atencional deve ser sustentado por um estado emocional de relaxamento também proporcionado pela prática de meditação, ocasionando em um estado interno de organização e concentração que diminuem as chances de possíveis interferências de gatilhos (156).

Desta forma, pensando na definição de atenção e em estudos prévios sobre o controle atencional, parece que o treinamento em mindfulness pode ser uma ferramenta eficaz para o controle atencional (83,157,158). Estudo realizado sobre o possível efeito da prática de mindfulness sobre o controle executivo revelou que a aceitação emocional e o monitoramento de desempenho são resultados encontrados após o treinamento desta prática. Segundo o estudo, a prática de mindfulness, ao trabalhar com a consciência do momento presente e a aceitação dos estados emocionais, acaba por manter e sustentar o controle executivo (159). Outro estudo de revisão sistemática sobre aspectos neuropsicológicos e treinamento em mindfulness encontrou como resultados significativos que a prática de mindfulness possibilita a melhora na atenção sustentada e executiva quando comparados a indivíduos com nenhum tratamento ou apenas com grupos de relaxamento. Outros resultados descritos estão relacionados a melhorias das funções executivas, incluindo inibição de respostas cognitivas, meta-cognição e auto-regulação do afeto (interferência emocional de estímulos que distraem) (160).

3.3.2 Viés atencional orientado para à ameaça

As teorias de base cognitivista defendem a ideia de um viés atencional voltado para a ameaça, sugerindo que os vieses de informações são características centrais para à etiologia e manutenção dos transtornos de ansiedade (54,55). Acredita-se que a ansiedade prejudica a eficiência do sistema atencional voltado a um objetivo e aumenta o processamento do sistema atencional dirigido a estímulos distratores relacionados a ameaça. Diversos estudos na área indicam que estímulos com valência negativa podem chamar mais a atenção em comparação aos estímulos positivos, sugerindo que a valência emocional é crucial para a captura automática da atenção (148–150). A apresentação de um estímulo aversivo altamente estimulante pode

provocar reações de fuga ou congelamento, ajudando o indivíduo a detectar a ameaça e promover a coleta de informações necessárias para a seleção de respostas.

Indivíduos ansiosos apresentam um viés seletivo para informações relevantes para sinais de perigo ou ameaça (161). Quando comparado a indivíduos não ansiosos, indivíduos ansiosos exibem uma tendência a interpretar estímulos neutros ou ambíguos como ameaçadores (viés de interpretação), têm maior facilidade em recordar eventos negativos (viés de memória) e para direcionar a sua atenção à estímulos ameaçadores sobre estímulos não-ameaçadores em seu ambiente (viés de atenção) (162). Em uma meta-análise com 172 estudos, incluindo indivíduos ansiosos e não ansiosos, estudo verificou que o viés de ameaça estava significativamente mais alto em indivíduos ansiosos, em diferentes paradigmas apresentados (65). Outro estudo investigou o efeito de estímulos distratores emocionais em uma tarefa Stroop de controle pró-ativo de atenção e sua relação com traços de ansiedade em uma amostra de 25 participantes com níveis baixos de ansiedade e 25 participantes com alta ansiedade. Os resultados indicaram que o grupo de participantes com alta ansiedade apresentou um controle pró-ativo da atenção reduzido e que a ansiedade influencia a interação entre estímulos emocionais irrelevantes e o controle atencional (129).

3.3.3 Vulnerabilidade emocional

O conceito de vulnerabilidade emocional está relacionado aos aspectos biológicos do desenvolvimento e da manutenção da desregulação emocional. A desregulação emocional pode ser definida como a falta de habilidade ou intensa dificuldade de inibir o comportamento emocional complexo, seja ele de valência positiva ou negativa e está relacionada à dificuldade de se autogerir para desenvolver ações coordenadas em direção a um objetivo externo e também conseguir alterar o foco atencional na presença de uma resposta emocional intensa. A teoria da regulação emocional postula três principais características da ansiedade: (1) mecanismos motivacionais e uma tendência a respostas emocionais, (2) mecanismos regulatórios e (3) consequências do aprendizado conceitual que reflete no repertório de comportamentos amplos e flexíveis (163).

Desta forma, o TAG apresenta-se como um transtorno com falhas em cada um destes sistemas normativos de funcionamento (111,164). O transtorno é caracterizado por intensa ansiedade e angústia que refletem em um maior efeito negativo de temperamento e ativação de sistemas motivacionais que buscam a obtenção de segurança. Consequentemente, este indivíduos, podem apresentar déficits em diferentes sistemas de regulação que contempla a

atenção (a flexibilidade atencional no processamento de estímulos emocionais); e estratégias cognitivas mais elaboradas (consciência, flexibilidade cognitiva e tomada de decisões). Ao contrário disso, os indivíduos com TAG utilizam estratégias perseverantes, tais como a ruminação, preocupação e autocrítica, para compensar a dificuldade de gerir suas emoções (165–167).

Nesse sentido, torna-se fundamental compreender que todos somos vulneráveis às nossas emoções, ou seja, todos nós temos um sistema de ativação emocional frente a estímulos emocionais. Ainda assim, alguns indivíduos apresentam maior vulnerabilidade ao seu processamento emocional, uma ativação mais sensível diante de estímulos, necessitando assim, de mais habilidade de/para modulação emocional(163,168,169).

A vulnerabilidade emocional envolve três componentes essenciais: a sensibilidade aumentada, a alta intensidade emocional e o retorno lento do estado emocional à linha basal (170). Os indivíduos com maior vulnerabilidade emocional tendem a responder de forma mais rápida diante de estímulos que possam suscitar uma resposta emocional. Com relação à alta intensidade emocional, observa-se que indivíduos vulneráveis apresentam um pico de ativação emocional mais alto, o que pode facilitar respostas extremas frente a estímulos disparadores da resposta emocional (163). Esse fenômeno ocorre devido ao processamento atencional diante de emoções mais intensas, onde os indivíduos apresentam dificuldade em modular a sua atenção, resultando em um foco aumentado em aspectos emocionais (154,156). Sobre o retorno lento ao estado de base, percebe-se que as reações emocionais de pessoas com maior vulnerabilidade emocional são mais longas. Essa característica expressa a dificuldade que esses individuos têm de voltar ao estado emocional, à linha basal, após passarem por alguma situação que os ative emocionalmente. Dessa forma, frente as ativações emocionais mais intensas, os indivíduos apresentam um maior foco atencional a estímulos geradores das respostas, como uma facilidade aumentada para recordar lembranças que sejam congruentes com as emoções atuais (163).

Mennin e Frasco (2013) (171), compilaram os estudos sobre terapia cognitivo-comportamental e ciência afetiva e propõem uma estrutura de ciência projetada para abordar a emocionalidade negativa associada ao TAG e a depressão. O modelo apresentado de desregulação emocional que caracteriza os transtornos de angústia está indicado como uma experiência emocional elevada que atua como uma estratégia compensatória para lidar com a vivência de situações emocionais e somáticas fortemente sentidas e que geram um intenso sofrimento no indivíduo. Este modelo terapêutico acredita que a desregulação emocional pode ser entendida por: 1) mecanismos motivacionais, que atuam sobre as respostas emocionais, 2) mecanismos reguladores, que exercem um papel na alteração de trajetórias de respostas

emocionais, utilizando menos os recursos atencionais e mais os recursos metacognitivos e 3) consequências contextuais da aprendizagem que possibilitam a promoção de repertórios comportamentais abrangentes e flexíveis. No TAG, a desregulação ocorre devido a uma falha em cada um destes sistemas de funcionamento. O modelo sugere que os pacientes se envolvam no desenvolvimento de habilidades de regulação emocional consciente para neutralizar o processamento disfuncional (uso da preocupação, ruminação, verificação e autocrítica) em direção da busca de comportamentos voltados a gratificações e objetivos importantes em suas vidas (172).

A modulação emocional não visa a modificação da valência da emoção (transformar raiva em alegria, por exemplo), mas frequentemente muda a sua dinâmica e intensidade (166). Estudos apontam a importância dos efeitos da regulação da emoção na vida das pessoas e a relevância desta função cognitiva para o bem-estar emocional (151,173). Alguns autores enfatizam a capacidade de flexibilidade e maleabilidade das respostas emocionais, habilidades estas que maximizam seu caráter adaptativo no enfrentamento de situações emocionais e aversivas (174). O uso disfuncional de estratégias de regulação da emoção está diretamente associado aos transtornos psiquiátricos (175–177).

Achados prévios sobre o uso da terapia de regulação emocional usando o formato de 20 sessões em uma população clínica, demonstraram a eficácia na redução de sintomas de ansiedade e depressão, junto com a preocupação e emocionalidade negativa reduzida e melhor regulação das emoções, com ganhos mantidos ao longo de 3 a 9 meses (178). Outro ensaio clínico randomizado apresentou redução dos escores de ansiedade e depressão, melhora nos níveis de bem-estar, qualidade de vida e funcionalidade, com ganhos mantidos por 9 meses após o tratamento (111).

3.4 Processos biológicos

3.4.1 Neutoanatomia do TAG

O TAG é caracterizado por estar associado a mudanças anatômicas no cérebro, particularmente dentro das regiões relacionadas ao neurocircuito de ansiedade. Estudos de neuroimagem identificaram anormalidades em regiões do cérebro e falhas de sincronização em pacientes com transtornos de ansiedade. Algumas regiões tipicamente associadas ao neurocircuito da ansiedade e regulação emocional são a hiperativação da amigdala (aumento do bottom-up) em respostas a ameaças ambientais e déficits no pré-frontal (diminuição do top-

down) para atenuação de respostas de medo induzidas pela amigdala (139). Juntamente, o córtex cingulado anterior, córtex pré-frontal medial, ventrolateral e dorsolateral também mostraram atividades alteradas ou anormais no TAG (179). Em consonância com isso, estudos encontraram aumento de matéria cinzenta na amigdala e um aumento da ativação da amigdala que se relacionada com a gravidade da ansiedade (180–182), principalmente em mulheres, o que resultou em tempos mais lentos de respostas em tarefas cognitivas, indicando déficit de atenção (183). Em tarefas de apresentação de faces emocionais, estudo observa a ativação da amigdala e do giro frontal médio em indivíduos com TAG (184). Anormalidades na regulação emocional e aprendizagem associativa são expressas através da atividade deficiente no córtex pré-frontal dorso-lateral e medial que são acionados durante atividade de reavaliação cognitiva de fotografias aversivas (185,186). Em paralelo, a capacidade diminuída do córtex pré-frontal ventro-medial (CPFvm) impossibilita a diferenciação de estímulos condicionados pelo medo de estímulos com características semelhantes, o que demonstra déficits na aprendizagem e processos de generalização de ameaças no TAG que podem contribuir para a origem do transtorno (187).

O TAG também está associado a uma diminuição da matéria branca no córtex pré-frontal dorsolateral e mesencéfalo o que está relacionado a uma maior gravidade dos sintomas e cronicidade da doença (188). Outras regiões como o CPFvm aparece envolvido no processamento de ameaças e perigos, associado com anormalidades no circuito corticolímbico e mesocorticolímbico em pacientes do sexo feminino que pode implicar nas vias dopaminégias envolvidas no TAG (189,190). A conectividade funcional no estado de repouso foi inferior pré-frontal límbico e cingulado e superior no hipocampo e ambas as anormalidades foram relacionadas a gravidade dos sintomas clínicos (191).

Em um nível neural, os mecanismos de regulação emocional estão associados a regiões do cérebro envolvidas em respostas emocionais e regiões ligadas a regulação da emoção. Um dos sistemas mais pesquisados é o formado pela amidgala e CPFvm que está envolvido na regulação amigdalar por meio das conexões baso-lateral da sub-região da amigdala (190,192). Na ansiedade, distúrbios relacionados a desequilíbrios nesse sistema ocasionam uma amigdala hiperativa que seria menos eficiente controlada pelo CPFvm. Alterações na conectividade dentro do circuito amigdala-préfrontal foram encontrados em estudos com pacientes ansiosos e grupos controle (168,169). Estudo avaliou a conectividade funcional em 28 pacientes com TAG e grupo controle com 28 sujeitos e encontrou uma maior conectividade no sistema amigdala-CPFvm esquerda em pacientes com TAG ((121). Outro estudo avaliou com 80 pacientes com TAG e 81 indivíduos saudáveis e observou que aqueles com TAG apresentaram maior

variabilidade no córtex pré-frontal dorsomedial bilateral (CPFdb) e hipocampo esquerdo apontando para alterações de conectividade em áreas sensório-motor e lobo límbico (193). Recente estudo avaliou a conectividade funcional em 74 sujeitos com TAG e 74 controles saudáveis através da ressonância magnética em repouso. Os indivíduos com TAG demonstraram diminuídos do hipocampo esquerdo, ínsula anterior esquerda, giro frontal esquerdo e giro-temporal inferior. O valor do hipocampo foi negativamente correlacionado com a Escala de Ansiedade de Hamilton (193),(194).

Algumas possibilidades de tratamento medicamentoso têm apresentado bons resultados para corrigir estas anormalidades no circuito da ansiedade. Uma melhor resposta ao tratamento com venlafaxina em pacientes com TAG foi associada com uma diminuição da ativação da amigdala na exposição de imagens aversivas e rostos temerosos (195,196). Junto a isto, entre os jovens com o transtorno, a melhora com o tratamento da fluoxetina também foi associada com uma menor ativação da amigdala na apresentação de tarefas cognitivas de pistas emocionais (197).

3.4.2 Sensibilidade interoceptiva

A sensibilidade interoceptiva é definida como a percepção de uma condição fisiológica do corpo, ou seja, uma percepção consciente dos processos emocionais e comportamentos relacionados às informações fisiológicas provenientes do corpo (198,199). Alguns mecanismos fisiológicos agem como estímulos interoceptivos, tais como a respiração, frequência cardíaca, pressão arterial ou atividade gastrointestinal. Algumas regiões do cérebro estão conectadas nesta rede neural de estímulos interoceptivos que vai da periferia ao sistema nervoso central, incluindo a ínsula, que está diretamente associada no processamento interoceptivo, bem como a amigdala, o hipotálamo e o córtex orbitofrontal. Essas regiões estão envolvidas na sensibilidade interoceptiva, assim como no circuito do medo (200,201). Estudos baseados nas teorias das emoções defendem a ideia de que a excitação desempenha um papel fundamental na formação das emoções através de marcadores somáticos do corpo que estão envolvidos em processos atencionais, de tomada de decisão e memória de trabalho (199,202).

A sensibilidade interoceptiva desempenha um papel fundamental na patogênese dos transtornos de ansiedade. Quando aferido, através de questionários de percepção somática, pacientes com TAG, frequentemente, relatam uma hipervigilância frente às sensações corporais (198,203), juntamente com flexibilidade autônomica diminuída e excitação basal elevada (204). Estes pacientes apresentam percepção de sensações somática e subsequente catastrofização

destas interpretações que estão relacionados aos estímulos interoceptivos ativos decorrentes do sistema cardíaco (205).

3.4.3 Variabilidade cardíaca

O comportamento e respostas autonômicas surgem da hierarquia da organização de diferentes sistemas filogenéticos do sistema autônomo com sistemas filogeneticamente mais novos que inibem os mais antigos. Esses processos são fundamentais para o comportamento adaptativo e maior variabilidade autonômica associado a respostas mais funcionais. Os déficits nestes processos são fatores de risco para a desregulação emocional e para o desenvolvimento de psicopatologias (206). O modelo neurovisceral, associado a regulação cardíaca e emocional, sugere ligações entre variabilidade cardíaca e transtornos de ansiedade através de uma rede central que conecta o sistema autonômico, atencional e afetivo, todos envolvidos na auto-regulação da emoção (207,208). Considerando este sistema, a variabilidade saudável implica a capacidade de reagir às demandas ambientais para manter a estabilidade do organismo. Entende-se que os transtornos de ansiedade apresentam um estilo de resposta rígido e inflexível que não são congruentes com as demandas do contexto. Os indivíduos ansiosos expressam uma incapacidade de inibir respostas ansiosas inadequadas em situações não-ameaçadoras mas que são percebidas por ele, como perigosas (16,166).

A Teoria Polyvagal apresenta uma nova perspectiva das relações entre o funcionamento anatômico e estados psicopatológicos de ansiedade e comportamento. A teoria inlui uma apreciação do sistema nervosos autônomo como um “sistema”, a identificação dos circuitos neurais envolvidos na regulação do estado autônomo e uma interpretação da atividade autônoma como adaptativa dentro do contexto da filogenia do sistema nervoso autônomo. Entende-se que a disfunção do sistema vagal pode levar a problemas de inibição, como déficits cognitivos e desregulação emocional (209,210).

O processo cognitivo subjacente no TAG é a preocupação, o qual têm sido associado a flexibilidade autonômica reduzida, como resultado do baixo tônus vagal cardíaco (89,137,201). Estudos epidemiológicos apontam que transtornos mentais como a ansiedade, a depressão maior, assim como o estresse estão associados a um aumento no risco cardiovascular (9,212). Além dos sintomas psicológicos e emocionais, o TAG é caracterizado por sintomas do sistema nervoso autônomo (SNA) que inclui sintomas de palpitações, ondas de calor, tremores e transpiração. O aumento do risco cardiovascular associado ao TAG pode estar associado à desregulação do SNA (9,213).

Diversos estudos têm apontado à diminuição VFC em pacientes com TAG, embora ainda existam controversas sobre o assunto (10,38). Uma recente meta-análise indicou que a medida do domínio da frequência da VFC é significativamente reduzida em pacientes com TAG em comparação com indivíduos saudáveis. O estudo sugere que o TAG afeta a regulação autonômica da homeostase cardiovascular, destacando os efeitos adversos sobre a reatividade do sistema nervoso parassimpático (38). Estudo realizado com 42 pacientes com TAG sem uso de medicação e 50 controles saudáveis mostrou que o transtorno está significativamente associado a menor variabilidade da frequência cardíaca, sugerindo que a integridade do sistema autonômico é substancialmente prejudicado nestes pacientes (216). Estudo longitudinal de depressão e ansiedade com dados de VFC e uso de antidepressivos avaliou, através de equações de estimativas generalizadas que a relação entre desregulação cardíaca e ansiedade, tornou-se insignificante após o ajuste para o uso de antidepressivo. Uma associação robusta foi encontrada entre o uso de antidepressivos (especialmente antidepressivos tricíclicos, ISRS e IRSN) e atividade cardíaca desfavorável em todas as ondas, confirmando que algumas associações provavelmente podem ser confundidas com o uso de antidepressivos (216). Estudo avaliou medidas de complexidade linear e não linear de VFC em 42 pacientes sem medicação com TAG e 50 controles saudáveis. O grupo com TAG apresentou desvio padrão significativamente menor nos intervalos RR e o valor aproximado de entropia, que é um indicador de complexidade não linear, também foi significativamente menor no grupo de pacientes do que no grupo controle (P, 0,01). Os achados mostram que o TAG está significativamente associado a redução da VFC e sugerindo que a integridade neurocardíaca autonômica está substancialmente prejudicada em pacientes com o transtorno (216).

Os possíveis mecanismos fisiopatológicos responsáveis por tais eventos são multifatoriais e controversos. Alterações na homeostase da função autonômica com um desequilíbrio entre os sistemas simpático e parassimpático seriam os principais envolvidos no risco cardiovascular aumentado (217,218). A análise da variabilidade da frequência cardíaca é um método não-invasivo, fácil de ser executado e reproduzível baseado no monitoramento por aparelho ECG que possibilita uma avaliação adequada do controle cardiovascular do sistema simpático/parassimpático (38).

A visualização de pistas desagradáveis está associada a desaceleração da frequência cardíaca (resposta de orientação) em comparação com pistas agradáveis ou neutras. Esses dados comparativos estão presentes em registros eletrofisiológicos de respostas sensoriais iniciais (145,219). Em uma amostra de 109 estudantes universitários com TAG e alto nível de preocupação, foi aplicado um teste objetivo de capacidade de controle top-down e VFC

mediada vagamente em repouso e medidas de autorrelato de crenças sobre a gravidade dos sintomas. Conforme esperado, os sintomas altos de ansiedade foram associados a crenças de que a preocupação tem utilidade e maior redução da VFC (220).

3.5 Modelos teóricos

Diversos modelos teóricos contemporâneos discutem sobre aspectos cognitivos que perpetuam e mantem o TAG. O primeiro é o *Modelo de Evitação da Preocupação*, que parte da premissa que as preocupações são formas verbais de linguagem que inibem imagens de cunho emocional negativo (24). Esta evitação emocional impede o processamento emocional do medo que é teoricamente importante para os processos de habituação e extinção que ocorrem na medida que o indivíduo se expõe aos estímulos emocionais (221,222). Sendo assim, o modelo acredita que a preocupação é uma estratégia ineficaz de lidar com possíveis ameaças e experiências emocionais aversivas. Na medida em que a preocupação é utilizada como um alívio imediato de emoções negativas, ela reforça o papel positivo da preocupação e a crença de que ela é útil na resolução de problemas, mas ao mesmo tempo, mantém o ciclo da ansiedade e do medo (24).

O *Modelo de Intolerância a Incerteza* enfoca na crença de que a preocupação será uma forma eficaz de lidar com possíveis ameaças e eventos futuros e, por vezes, evitar que tais situações temidas ocorram (223). Os indivíduos acometidos pelo TAG se sentem incapazes de lidar com as adversidades, através da crença de baixa auto-eficácia. Por vezes, são indivíduos pessimistas em relação ao futuro e descrentes das suas habilidades para lidar com aquilo que não se tem controle.

O *Modelo Metacognitivo* entende que os indivíduos com TAG são acometidos por dois tipos de preocupações (114,224). Quando o indivíduo está diante de uma situação que gera ansiedade, crenças positivas sob as preocupações são ativadas e ele acredita na eficácia dessa estratégia cognitiva para lidar com a situação (Preocupação do Tipo 1). No decorrer do curso da preocupação, crenças negativas sobre as preocupações são ativadas e o indivíduo passa a se preocupar sobre a preocupação (Metacognição), temendo perder o controle sobre este processo. Desta forma, o envolvimento em estratégias cognitivas ineficazes, como ruminação, verificações mentais, supressão de pensamento, distração e evitação seriam formas de lidar com a preocupação e, que, muitas vezes, os indivíduos percebem o quão disfuncional são, ativando crenças de insucesso de lidar com os problemas e também com a sua preocupação (Preocupação do Tipo 2) (224).

O *Modelo de desregulação de emoção* consiste em quatro componentes centrais; 1) inicialmente é entendido que os indivíduos com TAG sentem as emoções, tanto positivas como negativas, de forma mais intensa que a maioria das pessoas e tem um limiar inferior para lidar com emoções negativas (23,225) 2) são indivíduos que compreendem de forma mais pobre as suas emoções, com déficits importantes em descrever e rotular o que sentem; 3) eles têm atitudes mais negativas sobre as suas emoções quando se sentem estressados, ansiosos e sobrecarregados frente a emoções fortes. Por fim, 4) o modelo acredita que indivíduos com TAG apresentam estratégias disfuncionais de regulação e gestão das emoções, como a preocupação excessiva, supressão das emoções e ruminação, o que potencializa os estados emocionais negativos e a forma de percebê-los (23).

O último modelo é o *Modelo de transtorno de ansiedade generalizada baseado em aceitação* proposto por Roemer e Orsillo (2006) (226). Este é baseado no Modelo de evitação experiencial de Hayes e colegas (194). O modelo propõe que existe uma relação de fusão com as experiências internas (emoções, pensamentos, reações fisiológicas) e uma reação negativa frente ao aparecimento destas experiências. A partir disso, ocorre uma evitação experiencial, onde o indivíduo evita as experiências percebidas como ameaçadoras ou negativas. A preocupação é um exemplo deste funcionamento, no qual o indivíduo preocupa-se com possíveis eventos futuros ou preocupa-se com questões menores para evitar preocupações mais sérias. Considerando o nível comportamental, o resultado desse processo é uma restrição comportamental, onde o sujeito tem pouco envolvimento em atividades significativas, como ter tempo de lazer, descanso, momentos com família e amigos o que ocorre devido a evitação de suas experiências internas. A restrição comportamental pode ocasionar em redução da atenção ao momento presente, limitando a consciência do indivíduo quando este se envolve em situações prazerosas e com sentido. É comum que indivíduos com TAG tenham dificuldade em estar presente em momentos de descanso e lazer, na medida em que estão constantemente preocupados e hipervigilantes com qualquer situação. Roemer et al., (2005) evidenciam que indivíduos com TAG apresentam reações negativas frente às suas próprias experiências internas e tentam evitar sentir essas experiências. Esta evitação produz um alívio imediato e reduz o sofrimento causado em curto prazo, contudo, a evitação reforça a restrição comportamental e mantém o ciclo do TAG.

Apresentado os sintomas e sistemas de funcionamento do TAG, observa-se que a gênese do transtorno está associada a herdabilidade de fatores genéticos e o restante contabilizado pelo ambiente, neurofisiologia e temperamento que também tem uma carga genética (119). E que todos esses componentes vão gerar uma vulnerabilidade cognitiva que predispõem o indivíduo

a aumentar ou diminuir a resposta ansiosa frente a alguma situação ou agente estressor. A manutenção do transtorno decorre das interpretações catastróficas sobre os eventos e previsões negativas acerca de si, do mundo e do futuro, o que ocasiona em comportamentos de evitação e uma desregulação emocional (226).

3.6 Tratamento

A maioria das diretrizes de tratamento psicofarmacológico para os transtornos de ansiedade recomendam os inibidores de receptação de serotonina (ISRS) e inibidores de receptação de serotonina e norepinefrina (IRSN) e pregabalina como tratamento farmacológico de primeira linha para o TAG devido a sua eficácia e bons perfis de segurança (70,72,74,227). De acordo com estas diretrizes, os benzodiazepínicos não são recomendados como tratamento de primeira escolha devido aos efeitos colaterais e a dependência associada ao longo prazo. Entretanto, esta classe farmacológica pode ser usada por um tempo limitado em certas circunstâncias, como no início do tratamento por exemplo (119,228). Ainda assim, uma proporção de pacientes com TAG não apresenta uma melhora significativa com este tratamento de primeira linha, sendo que cerca de 50 a 60% respondem ao tratamento medicamentoso e os demais, permanecem com sintomas residuais, com alto risco de cronicidade do transtorno e uma baixa qualidade de vida (71,229).

Uma revisão sistemática e meta-análise em rede foi realizada em ensaios clínicos randomizados em pacientes com TAG incluindo 89 estudos (n= 25.441) designados aleatoriamente para 22 medicamentos ativos ou placebo. A duloxetina, pregabalina, venlafaxina e escitalopram foram mais eficazes que o placebo apresentando boa aceitabilidade. A quetiapina teve o maior efeito sob Hamilton Anxiety Rating Scale o (HAM-A), mas foi mal tolerada. Da mesma forma, a paroxetina e os benzodiazepínicos foram eficazes, mas também pouco tolerados em comparação com o placebo (72). Recente meta-análise com 234 estudos comparou os diferentes tratamentos para os transtornos de ansiedade (TAG, Fobia Social e Transtorno do Pânico). Os medicamentos foram associados a um tamanho de efeito pré-pós tratamento significativamente mais alto [(Cohen´s d= 2.02 (1.90-2.15)] comparado as psicoterapias [(Cohen´s d= 1.22 (1.14-1.30)]. O tamanho de efeito foi de 2.25 nos inibidores de recaptação de serotonina-noradrenalina (n= 23 braços do estudo), 2.15 nos benzodiazepínicos (n= 42), 2.09 para os ISRS (n=62) e 1.83 para antidepressivos. Em comparações diretas nos grupos controles, todos os medicamentos, exceto o citalopram e opipramol, foram significativamente mais eficazes que o placebo, assim como a TCC mais eficaz que a lisa de espera (227). Meta-análise

sintetizou estudos de intervenções para TAG através de 91 ensaios clínicos randomizados (n= 14.812 participantes). Os resultados mostraram que todos os tratamentos farmacológicos, exceto moduladores de serotonina e antipsicóticos de segunda geração, tiveram efeitos maiores que placebo: inibidores de receptação norepinefrina-dopamina (diferença da média padronizada), 1,84, intervalo de confiabilidade (95% -3,05 a -0,62), noradrenérgicos e antidepressivos serotonérgicos (-0,91, -1,62 a -0,20), antagonistas do receptor melatonérgico (-0,68, -1,15 a -0,21), ISRS (-0,67, - 0,90 a 0,43), IRSN (-0,54, -0,79 a -0,30) e benzodiazepínicos (-0,40, -0,65 a -0,15). A maioria das intervenções psicológicas e de auto-ajuda exerceu efeitos maiores que a lista de espera, contudo, as intervenções farmacológicas tiveram tamanhos de efeitos maiores que as intervenções psicológicas (230). Revisão sistemática com intervenções controladas para pacientes com TAG adultos (27 ensaios randomizados, n= 2373) não encontrou diferenças significativas nos grupos quando comparados. Os efeitos do tratamento farmacológico (OR= 0.32, IC= 95%: 0,18-0,54) e tratamento psicoterapêutico (OR=0.33, IC= 95%: 0,17- 0,66) foram semelhantes, com resultados favorecendo intervenções ativas sobre controle (231).

No que tange ao tratamento psicoterápico, um número considerável de pesquisas foi desenvolvido ao longo das últimas décadas comprovando a TCC como tratamento eficaz para os transtornos de ansiedade (95,119,161,232,233). Os protocolos de TCC são baseados em estratégias terapêuticas como a psicoeducação, a reestruturação cognitiva e as técnicas de exposição que visam a modificação de crenças disfuncionais e exposição a situações e pensamentos temidos (108,161,235). Para os transtornos de ansiedade, os modelos cognitivos postulam que a avaliação exagerada da ameaça é um elemento central subjacente a ansiedade patológica (66,161). Na TCC, os pacientes são estimulados a identificar pensamentos automáticos que mantém a ansiedade para então desenvolverem estratégias mais funcionais para lidarem com a ansiedade.

Em 2008, foi publicada a única meta-análise de ensaios randomizados e controlados por placebo de TCC para transtornos de ansiedade. Identificou-se 27 estudos que mostraram efeitos moderados a grandes da TCC para a redução dos sintomas de ansiedade (Hedges´g= 0,73) (17). Outra meta-análise incluiu um total de 41 estudos (n = 2132 indivíduos com TAG) avaliou o efeito da TCC em comparação a um grupo controle. O efeito combinado de 38 comparações (28 estudos) de psicoterapia versus grupo controle (grande maioria como lista de espera) foi grande (g=0,34; IC de 95%: 0,71-0,97) com heterogeneidade baixa a moderada (108). Recente meta-analise (235), avaliou a eficácia da TCC nos transtornos de ansiedade com base em 41 ensaios clínicos randomizados com placebo (n= 2835 sujeitos). As intervenções que usaram de

estratégias de exposição tiveram um tamanho de efeito maior do que as técnicas cognitivas e comportamentais. Revisão sistemática avaliou ensaios clínicos randomizados com medida de efeito o tratamento de TCC em adultos e idosos Os resultados demonstraram tamanho de efeito grande nos sintomas no TAG (Hedges´ g=1.01). Os 14 estudos incluídos (n=772) o tamanho de efeito ao final do tratamento de TCC em comparação a qualquer controle foi médio e a favor da TCC (g=0,66; IC de 95%; 0,42-0,90) (78).

Outra possibilidade de abordagem terapêutica é o treinamento de atenção plena. O termo "atenção plena" descreve uma maneira particular de prestar atenção ao momento presente através de uma atitude receptiva e não julgadora (236). Esse termo é frequentemente usado para descrever um tipo particular de práticas de meditação que trabalha com a premissa de que, ao invés da evitação ou supressão de uma experiência negativa, o indivíduo pode encontrar uma maneira mais efetiva de lidar com as experiências através da aceitação experiencial. A atenção plena guia o indivíduo ao ajuste de processos e padrões cognitivos envolvidos no TAG (86). Intervenções baseadas em atenção plena aumentaram a sua popularidade e eficácia para o tratamento da ansiedade nos últimos anos (160). Como recurso terapêutico, as práticas meditativas têm sido associadas a regulação emocional (80,176). Entre elas, o mindfulness, que é descrito como uma prática do budismo, é compreendido como uma prática sistematizada para a tomada de consciência e capacidade de atenção ao momento presente, sem julgamento (236). A prática de mindfulness traz benefícios para tratamentos psiquiátricos, doenças neuropsiquiátricas, distúrbios de saúde, redução dos níveis de cortisol (81,237,238).

Diversos estudos recentes sugerem que o treinamento em mindfulness pode mudar a morfologia do cérebro, particularmente nas áreas relacionadas a atenção e seleção de respostas (239,240). Estudos prévios de neuroimagem sob os efeitos do mindfulness em áreas cerebrais verificaram que, durante a apresentação de tarefas de conteúdo emocional, houve aumento da ativação do CPF bem como a inibição da atividade da amígdala (241,242). Em outro estudo, áreas cerebrais como córtex pré-frontal, áreas da ínsula anterior direita, associadas com atenção, sensopercepção eram mais densos nos meditadores do que nos controles (243).

Estudo de intervenção realizado com 20 meditadores e um grupo controle avaliou, através da apresentação de imagens de conteúdo positivo e negativo, o efeito do mindfulness e os dados comportamentais, assim como o registro da atividade eletrocardiográfica revelaram uma associação da prática com controle atencional e emocional (244). Um ensaio clinico randomizado com pacientes com TAG que recebeu o protocolo de redução de estresse baseada em mindfulness (MBSR) em comparação com um grupo de controle ativo de atenção observou que os participantes que receberam o MBSR para a redução de sintomas de ansiedade tiveram

redução de concentração de ocitocinas inflamatórias. O estudo sugere, então, evidências imunológicas que o programa de mindfulness pode aumentar a resiliência ao estresse e diminuir sintomas de ansiedade (82,245).

Outra possibilidade de tratamento são os grupos terapêuticos que têm como principal função a educação em saúde e melhora na capacidade do indivíduo em alcançar qualidade de vida e redução de sintomas. Estudos apontam que estilos de vida promotores de saúde se caracterizam como comportamentos que os indivíduos tomam a iniciativa de realizar algo que pode beneficiar a sua saúde. Os componentes das ações de promoção de saúde incluem: responsabilidade pela saúde, atividade física, nutrição, relacionamentos pessoais, crescimento espiritual e manejo do estresse (246).Estudos indicam que pessoas que se dedicam para ter um estilo de vida mais saudável, conseguem alcançar uma melhor saúde física e emocional (247,248).Os resultados das pesquisas ainda são inconsistentes, embora a maioria deles indique uma relação positiva entre a prática de exercício físico e satisfação com a vida e bem estar físico e emocional (249,250).

O processo grupal em promoção de qualidade de vida possibilita, além do aprendizado, a socialização, a integração, o apoio psíquico e a troca de experiências. O uso de grupos para a promoção de qualidade de vida é um dos férteis campos para promover a autonomia e a funcionalidade do sujeito (251). Indivíduos com ansiedade podem se beneficiar destes grupos através da psicoeducação e mudanças no estilo de vida e em componentes que estão associados a redução da ansiedade. São apresentadas informações teóricas e práticas no intuito de promover, prevenir e educar o indivíduo sobre saúde e bem-estar e o capacitar a aplicar tais ferramentas no seu cotidiano com o objetivo de diminuir os sintomas de ansiedade (252,253).

4 OBJETIVOS

4.1 Objetivo geral

Avaliar, em pacientes com TAG, a capacidade de controle atencional e emocional e relacionar estes dados com a variabilidade cardíaca pré e pós- intervenção em três grupos de intervenção (mindfulness, medicação e qualidade de vida).

4.2 Objetivos específicos

Avaliar a capacidade de controle atencional e emocional dos participantes no baseline e após intervenção: mindfulness, qualidade de vida e medicação.

Correlacionar os dados de variabilidade cardíaca com o funcionamento cognitivo e emocional durante realização de tarefa cognitiva nos pacientes com TAG.

Apresentar um protocolo de mudança de hábitos para promoção de qualidade de vida e testar sua eficácia.

5 DESFECHOS

O desfecho primário (ajustado para possíveis fatores de confusão) é a eficácia clínica das três intervenções aplicadas no controle atencional e emocional que foi avaliada pela Tarefa de Discriminação no início e no final do tratamento (semana 8) e a associação com a variabilidade cardíaca. Desfechos secundários incluíram a avaliação de escalas HAM-A, HAM-D, WHOQOL, DERS, PSQW e análise do grupo controle de qualidade de vida. Todas as medidas de resultados foram avaliadas no início do estudo, na semana 5 e no final do tratamento (semana 8).

6 METODOLOGIA

6.1 Delineamento

Ensaio clínico randomizado cegado avaliando mecanismos cognitivos, emocionais e biológicos em pacientes com TAG pré e pós intervenção nos três grupos de tratamento: mindfulness, medicação e grupo de qualidade de vida. O estudo está vinculado a um estudo maior, já publicado, intitulado: “Um ensaio clínico randomizado comparando a eficácia de uma abordagem baseada na atenção plena com um grupo de comparação ativo e tratamento com fluoxetina para adultos com TAG”.

6.2 População do estudo

Pacientes com TAG recrutados através da mídia.

6.3 Critérios de inclusão

- ✓ Ter mais de 18 anos;
- ✓ TAG primário diagnosticado pelo Mini-International Neuropsychiatric Interview (M.I.N.I);
- ✓ Possibilidade de ir semanalmente, por 8 semanas.

6.4 Critérios de exclusão

- ✓ Estar em tratamento psicofarmacológico ou psicoterápico.
- ✓ Falha a um tratamento prévio com fluoxetina ou intolerância prévia à mesma.
- ✓ Transtorno Bipolar, Transtorno Psicótico, Transtorno por Uso de Substância (exceto Tabaco) nos últimos 6 meses ou Ideação Suicida nos últimos 6 meses (M.I.N.I)
- ✓ HAM-D≥23
- ✓ Ter contraindicação ao uso de ISRS (uso de tioridazina ou IMAO, coagulopatia ou uso de anticoagulante, uso de terapia antirretroviral) ou MBI (instabilidade clínica ou imobilidade)
- ✓ Estar em Gestação ou Lactação
- ✓ T. Personalidade Antisocial

7 PROCEDIMENTOS

Todos os participantes foram avaliados por um grupo de psicólogos e psiquiatras com treinamento para os instrumentos utilizados antes do ingresso do estudo e durante as avaliações. Os sujeitos selecionados após a triagem telefônica foram submetidos a uma entrevista clínica diagnóstica estruturada (MINI) e uma avaliação, através dos instrumentos e medidas clínicas descritos abaixo. Todos os sujeitos foram avaliados clinicamente antes e após a intervenção, através de questionários auto-aplicáveis e também na tarefa cognitiva.

8 INSTRUMENTOS DE PESQUISA

8.1 Medidas Sociodemográficas

Avaliação do nível sociodemográfico foi realizada através do critério de classificação econômica Brasil/2015.

8.2 Mini-International Neuropsychiatric Interview (M.I.N.I.)

O M.I.N.I consiste em uma entrevista diagnóstica estruturada e validada que permite ao pesquisador fazer diagnósticos psiquiátricos baseados no DSM-IV e na CID-10 (244). Apresenta versão traduzida, adaptada e validada para o português brasileiro. Para o presente estudo, os pesquisadores realizaram adaptações para contemplar o DSM 5.

8.3 Hamilton Anxiety Rating Scale (HAM-A)

É uma escala de 14 itens amplamente utilizada e validada, desenvolvida para quantificar a gravidade dos sintomas de ansiedade (255,256). Apresenta aspectos satisfatórios na validade e fidedignidade para a população brasileira (257).

8.4 Hamilton Rating Scale for Depression (HAM-D)

É uma escala de 21 itens considerada como "padrão ouro" para avaliar a severidade de sintomas depressivos (255,258). A validação brasileira apresenta coeficientes de confiabilidade e evidências de validade discriminante e convergente (258,259).

8.5 WHOQOL-Bref

É uma escala validada para a população brasileira composta de 26 questões que mede a qualidade de vida, divididas em 4 domínios: físico, psicológico, de relações sociais e do meio ambiente. Apresenta características satisfatórias com relação à consistência interna, validade discriminante, validade concorrente, validade de conteúdo e confiabilidade teste-reteste (260).

8.6 Difficults in Emotion Regulation Scale (DERS)

É um instrumento que avalia níveis de desregulação emocional em seis domínios: não aceitação das emoções negativas; incapacidade de se envolver em comportamentos dirigidos por objetivos quando experiencia emoções negativas; dificuldades em controlar comportamento impulsivo quando experiencia emoções negativas; acesso limitado a estratégias de regulação emocional que são percebidas como efetivas; falta de consciência emocional; e falta de clareza emocional. As propriedades psicométricas da versão em português do Brasil do DERS indicaram boa consistência interna (261).

8.7 Penn State Worry Questionnaire (PSWQ)

É uma escala autoaplicável desenvolvida para medir o traço preocupação (262,263) contendo 16 itens do tipo likert, com pontuação de 1 a 5 na qual avalia a generalidade, excessividade e incontrolabilidade da preocupação, com boa capacidade de discriminar indivíduos com TAG. A avaliação psicométrica da versão em português manteve adequada consistência interna (264).

9 TAREFA COGNITIVA

O Discrimination task foi usado como tarefa cognitiva. Este instrumento foi desenvolvido para avaliar os efeitos da aversão a imagens sobre o desempenho em uma tarefa simples de discriminação de estímulos (157). O uso de uma tarefa cognitiva e imagens emocionais no parâmetro EI avalia como os indivíduos inibem as respostas a estímulos emocionais quando comparado a estímulos neutros, sugerindo que o desempenho nestas tarefas cognitivas são mediadas pela percepção e processamento de estímulos emocionais.

O teste consiste na apresentação de diferentes imagens centrais na tela do computador e barras laterais com diferentes inclinações. Os sujeitos foram orientados a ignorar as imagens que apareciam no centro da tela e responder o mais rapidamente se as barras laterais encontravam-se na mesma inclinação ou não. Um treino foi realizado previamente ao início do teste. A tarefa foi dividida em três blocos de diferentes níveis de dificuldade apresentado aleatoriamente. Nos dois blocos difíceis, a orientação das duas barras diferia em apenas 12 °, enquanto no bloco fácil, a orientação das barras diferia em 90 °. Duas classes de imagens foram empregadas: imagens neutras e imagens emocionais/desagradáveis. As imagens neutras consistiam em fotografias de pessoas e as imagens desagradáveis em fotografias de corpos mutilados. Foram utilizadas 120 diferentes imagens, 60 neutras e 60 desagradáveis. Destas imagens, 42 imagens foram retiradas do International Affetive Picture System (IAPS) e as demais foram obtidas na internet (265). O tempo de reação (RT) e os erros foram registrados para cada tentativa. E o tempo de duração média do teste foi de 20 minutos. Foi utilizado o software E-prime.

10 MEDIDA CLÍNICA

Variabilidade Cardíaca

Adicionado a tarefa cognitiva, medimos a VFC nos pacientes em uma sala com atenuação de som e luz e os instruímos que se sentassem em uma posição confortável, onde eles tiveram o seu 3º dedo da mão esquerda ligado a um aparelho capaz de realizar a leitura dos intervalos inter-batimentos (IBI) que é ligado a um computador. Os IBI, que são substitutos dos intervalos R-R (duração de tempo entre duas ondas R do ECG), foram usados para a análise da VFC por um *software* nesse computador. Os dados da VFC foram medidos em um ponto de tempo aleatório variando da manhã a tarde, dependendo da disponibilidade dos pacientes se dirigirem ao hispital. Depois, foi avaliado os dados de pletismografia de pulso (PPG) usando um Shimmer3 GSR com o sensor óptico de pulso conectado ao segundo e terceiro dedos da mão esquerda. As frequências de aquisição foram de 512 Hz para as três primeiras ondas de estudo e 65,5 Hz na última onda. As frequências de aquisição não foram correlacionadas com a VFC em nosso estudo. A medida de variabilidade cardíaca foi realizada em repouso e durante a execução da tarefa cognitiva Discrimination Task.

11 INTERVENÇÃO

11.1 Body in Mind Training (BMT)

Este é um protocolo de MBIs que foi desenvolvido por uma pesquisadora do *King´sCollege London*, Ph. D. Tamara A. Russell (80,266). Consiste em uma intervenção em grupo com 10-15 participantes. O objetivo é capacitar os participantes no desenvolvimento de habilidades de *Mindfulness* através de exercícios que promovem autoregulação atencional, emocional, proprioceptiva, além do treinamento de autocompaixão. As práticas foram ensinadas durante um encontro semanal de duração de 120 minutos durante 5 semanas. Os pacientes são incentivados a integrar as práticas aprendidas no grupo no seu cotidiano, por pelo menos 20 minutos diários, sendo progressivamente integradas às demais práticas que serão ensinadas nas semanas posteriores. A condução deste grupo foi realizada por um pesquisador que realizou treinamento formal no método BMT durante seu estágio de doutorado no exterior com a prof. Tamara A. Russell

BMT sessão 1 - PAUSA: psicoeducação sobre a importância de pausar e desacelerar no dia-a-dia; exercício da uva-passa (comer lentamente uma uva-passa); exercício de sentar-se e concentrar nas sensações corporais e respiração; compartilhar em grupo; exercício de movimentar o pescoço para esquerda e direita, lentamente; psicoeducação; final.

BMT sessão 2 - INTENÇÃO: psicoeducação sobre a importância de observar a intenção de mover-se no dia-a-dia; exercício da caminhada meditativa; compartilhar em grupo; psicoeducação sobre o cérebro e o estresse; exercício de escaneamento corporal sentado na cadeira; compartilhar em grupo; psicoeducação; final.

BMT sessão 3 – ATENÇÃO: psicoeducação sobre como funciona a nossa atenção; exercício do espaço de 3 minutos de respiração; compartilhar em grupo; exercício de atenção aos sons do ambiente mesclado com atenção a respiração; compartilhar em grupo; psicoeducação; final.

BMT sessão 4 – UM CIENTISTA EM MIM: psicoeducação sobre como funciona nossa atenção; exercício do espaço de 3 minutos de respiração; compartilhar em grupo; exercício de atenção aos sons do ambiente mesclado com atenção na respiração; compartilhar em grupo; psicoeducação; final.

BMT sessão 5 – AUTOCOMPAIXÃO: psicoeducação sobre a importância de estados de aceitação e flexibilidade psicológica; exercício de desenvolvimento de autocompaixão (*be friending technique*); compartilhar em grupo; final.

BMT sessão 6, 7, 8: espaço destinado a práticas previamente aprendidas em grupo

11.2 Grupo Controle 1 - Fluoxetina

O grupo controle recebeu indicação de tratamento farmacológico com fluoxetina, medicamento disponibilizado na rede pública de saúde. Os pacientes foram orientados a iniciar com 20mg na primeira semana, podendo, após terceira semana, aumentar para 40mg conforme a resposta e a tolerabilidade. Os pacientes receberam acompanhamento semanal por psiquiatra durante as 8 primeiras semanas.

11.3 Grupo Controle 2 – Grupo Qualidade de Vida

Composto por 8 sessões semanais, conduzidas por psicólogo, com duração de 2 horas. Os tópicos discutidos eram temas relevantes para o manejo da ansiedade em geral.

GQV sessão 1: Psicoeducação da TAG

GQV sessão 2: Uso de substâncias

GQV sessão 3: Higiene do sono

GQV sessão 4: Atividade física

GQV sessão 5: Alimentação saudável

GQV sessão 6, 7 e 8: espaço destinado a discussões referentes as mudanças de hábitos adquiridas.

12 CÁLCULO DO TAMANHO AMOSTRAL

Considerando-se o poder de 90%, um nível de significância de 0,05, usando como referência o artigo (157) que encontrou um desvio padrão do grupo de meditação para a variável ansiedade de 2.0 e 2.1 para o grupo controle ativo, a estimativa do cálculo amostral foi de n= (162), ou seja (54 por grupo). Foi utilizado o WINPEPI V11.43.

13 ASPECTOS ÉTICOS

Este estudo esteve de acordo com as Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos (Resolução 196/96) e foi aprovado pelo Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre (número do projeto: 20160301). Todos os participantes estiveram de acordo com os objetivos da pesquisa e assinaram o termo de consentimento livre e esclarecido antes da participação no estudo.

Todos os dados foram mantidos em local considerado seguro pelos responsáveis do projeto, garantindo os direitos de privacidade dos entrevistados. Apenas os membros da equipe, diretamente ligados à pesquisa, tiveram acesso e manusearam os dados coletados. Os itens referentes ao sigilo das informações coletadas foram garantidos pela não identificação dos sujeitos. Os sujeitos foram igualmente informados sobre a possibilidade de divulgação/publicação dos dados fornecidos, resguardando a sua privacidade.

14 ARTIGOS

14.1 Artigo 1

Publicado no Journal of Psychiatric Research

Heart Rate Variability as a Predictor of Improvement in Emotional Interference in Generalized Anxiety Disorder

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Abstract

Background

Generalized anxiety disorder (GAD) is one of the most prevalent anxiety disorders but the least successfully treated. The search for accessible clinical, psychological and biological markers is crucial for developing more effective and personalized interventions. **Aims**: To evaluate if changes in heart rate variability (HRV) between rest and stress conditions before interventions could predict improvement in emotional interference (EI) in a cognitive task after three different treatment modalities in patients with GAD. **Method:** This is a post-hoc analysis study reporting data from a larger randomized controlled trial (NCT03072264) assessing a mindfulness-based intervention (BMT), fluoxetine (FLX), and an active comparison group (QoL) in adult patients diagnosed with GAD. We assessed pulse plethysmography (PPG) data using a Shimmer3 GSR to measure HRV. Regression analyses were performed using the variation between baseline and endpoint EI scores as dependent variables and contrasts considering changing in HRV*group interaction in the baseline. **Results:** 106 individuals were included.

The correlations between HRV changing from rest to task predicted improvement in IE only in the FLX versus control group contrast (estimated = −80.24; SE = 27.31; p = 0.005) and not in the BMT and control group contrast. **Conclusion:** More flexible HRV at baseline predicted EI improvement only in the FLX group. This finding is clinically relevant since it may help us develop more personalized interventions for GAD.

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Keywords: heart rate variability; anxiety. mindfulness; worry; emotional interference.

1 INTRODUCTION

There is a growing need for objective clinical, psychological and biological predictor measures in psychiatry. Heart rate variability (HRV) is a clinically relevant and easily measurable biological component that mirrors the function of different systems such as the autonomic nervous system and central nervous system regions (McCraty & Shaffer, 2015). Its simple measurement during rest can predict an organism's regulatory capacity (McCraty & Shaffer, 2015), and even overall mortality (Dekker et al., 1997). A reduced HRV is associated with different psychiatric conditions (Agelink et al., 2002; Chalmers et al., 2014; Kemp et al., 2014; Shah et al., 2013), whereas a higher HRV is associated with a more adaptive response to emotional stimuli. Low resting vagal tone and reduced HRV is reported in patients with Generalized Anxiety Disorder (GAD) (Christou-Champ et al., 2015). GAD presents worry as a core symptom (Chang et al., 2019; Kemp et al., 2014, Levine et al., 2016), and psychological mechanisms such as emotional dysregulation. Neuroimage studies corroborate the important role of HRV in GAD since individuals with low HRV may have difficulties in recruiting prefrontal brain areas necessary for amygdala modulation in emotional regulation activity (Geister, 2010; Steinfurth et al. 2018).

Emotional interference (EI) during tasks is an objective measurable of psychological processes in GAD. Anxiety is associated with deficits in cognitive attention and emotional regulation process (Cuthbert & Insel, 2010; Mennin & Fresco, 2013), resulting in hypervigilance for signs of threat, increasing perceptions of danger, and emotional dysregulation (Gross, 2013; Newman, 2011). Studies showed hypoactivation of the prefrontal cortex during the regulation of emotion (Ball et al., 2013). A recent review evaluating HRV and emotional dysregulation reported changes in cardiological data such as decreased HRV and increased LF/HF ratio in individuals with anxiety when exposed to aversive emotional images (Shu et al., 2018). Moreover, Azevedo et al. (2005) showed that the exposure to a set of

photographs of mutilated bodies promotes sustained bradycardia several seconds after the stimulus disappears (Azevedo et al., 2005). To assess and evaluate EI and its association with GAD and HRV may allow for a better understanding of the disorder and add to the evaluation of clinical and biomarkers that may predict intervention response.

Despite its high prevalence, GAD is still the least successfully treated anxiety disorder (Newman et al., 2013). To identify objective clinical and biological predictors of outcome may be crucial for development of more personalized treatments. This study aims to assess whether the baseline change in HRV from the rest to the task condition predicts improvement in EI in a cognitive task after a trial with three different modalities of treatment (Body in Mind Training, BMT; fluoxetine, FLX; an active control group, QoL) in a sample of patients diagnosed with GAD. Since healthy individuals with trait and state anxiety had a decreased HRV response to a psychological task (Shinba et al., 2008), and studies suggest that heart function might play a role in modulating cognitive performance via afferent pathways (McCraty & Shaffer, 2015), we hypothesized that individuals with more flexible system characterized by more changes in HRV from rest to a task at baseline would better improve their EI after BMT and FLX trial, when compared with QoL intervention.

2 METHODS

2.1 Design

This study is a post-hoc analysis reporting data from a randomized controlled trial (Costa et al., 2020) assessing BMT (Russell, 2011; Russell T.A. & Tatton-Ramons T., 2014) and FLX treatment compared to an active control group (Quality of Life and Psychoeducation, QoL) in adult patients diagnosed with GAD for eight weeks. We delivered all interventions (BMT and QoL) in a group weekly 2-hour session. More details in the study design can be found elsewhere (Costa et al., 2020).

2.2 Sample and Setting

We recruited the participants through media advertisements from the community and screened them by phone call through a brief assessment of GAD symptoms (Generalized Anxiety Disorder 7-item scale, GAD-7). Details in the sample selection are described in Costa el al (ref), but briefly, we confirmed psychiatric diagnoses according to the Mini-International

Neuropsychiatric Interview (M.I.N.I.) adapted to DSM-5 criteria. Inclusion criteria were adults (aged 18 or older), primary GAD diagnosis, availability to attend the sessions, and no current treatment for anxiety symptoms. The main exclusion criteria were Hamilton Depression Rating Scale (HAM-D) score ≥23, comorbidities as lifetime bipolar disorder, lifetime psychotic disorder, current eating disorder, current antisocial personality disorder, substance use disorder (except tobacco) in the last six months, and suicidal ideation during the previous six months. All participants gave their written informed consent after the interview (Ethics Committee of Hospital de Clínicas de Porto Alegre, number 20160301). The trial was registered at ClinicalTrials.gov (NCT03072264).

2.3 Measures

Clinical Measures:

Mini-International Neuropsychiatric Interview (M.I.N.I.)

M.I.N.I. is a structured clinical diagnostic interview to assess psychiatric diagnoses based on DSM-IV and CID-10 (Sheehan et al., 1998). We used the validated version for the Brazilian population (Amorim, 2000) assessed by trained professionals.

Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a clinician-rated and well-validated rating scale to evaluate the severity of anxiety symptoms (Hamilton, 1959). This scale comprises 14 items rating from zero (no symptom) to 4 (the worst severity symptom) (Hamilton, 1959). The total score ranges from 0 to 56. Blinded evaluators for the participants' intervention (BMT, FLX or QoL) performed this assessment.

Penn State Worry Questionnaire (PSWQ)

PSWQ is a self-report rating scale developed to measure worry (Meyer et al., 1990) and it is validated for the Brazilian population (Castillo et al., 2010). It comprises 16 items ranging from 1 to 5 with an adequate ability to discriminate individuals with GAD (Meyer et al., 1990). The total score ranges from 16 to 80.

Generalized Anxiety Disorder 7-item (GAD-7) Scale

The GAD-7 is a brief, self-report screening scale with seven items (23) and it is validated for the Brazilian population (38). The total score ranges from 0 to 21.

Difficult in Emotion Regulation Scale (DERS)

DERS is a self-rated 5-point Likert scale that assesses levels of emotional dysregulation. It contains 36 items ranging from 1 to 5 each (Gratz & Roemer, 2004). Higher scores indicate

worse levels of emotion regulation. It has a Portuguese version validated for being used in Portugal (Coutinho et al., 2010), and we adapted the instrument for Brazilian population.

Heart Rate Variability

We collected HRV data at baseline before treatment. We evaluated the subjects in a sound and light attenuated room and instructed them to sit in a comfortable position for five minutes. We measured HRV data in a random time-point ranging from morning to afternoon depending on patients' preference for coming to the hospital. Afterward, we assessed pulse plethysmography (PPG) data using a Shimmer3 GSR with the optical pulse sensor attached to the left hand's second and third fingers. Acquisition frequencies were 512Hz for the first three study waves and 65.5Hz in the last wave. Acquisition frequencies were not correlated with HRV in our study. Data was transferred to the Consensys software and exported for analysis. PPG signal was inspected for artifacts by algorithm, filtered using a standard Butterworth filter, and processed using the PhysioNet Cardiovascular Signal Toolbox (Vest et al., 2018) in MATLAB R2017b. We excluded inter-beat intervals that varied by more than 20% from the median five intervals before and after or that were deemed nonphysiological (IBI > 2s or < 0.375s). We calculated high-frequency heart rate variability using the root mean square of successive differences between inter-beat intervals. Two 120s intervals were extracted for HRV measurement: a rest condition, in the 120s immediately before task onset, and a task condition, 420s into the task (Electrophysiology, 1996). Both intervals lasted 120s. Furthermore, we obtained an HRV percent variation between rest and task conditions for each subject.

Cognitive Discrimination Task

This instrument was developed to evaluate the effects of aversive images on performance in a simple stimulus discrimination task (Menezes et al., 2013; Erthal et al., 2005). In each trial, we presented a neutral or aversive image in the center of a computer screen, flanked by two bars with different orientations. We instructed the participants to ignore the images and indicate, as quickly as possible, whether or not the bars were oriented in the same direction. In each trial, a fixation cross was shown at the center of the screen for 1500 ms, followed by the central image (size: 9° x 12°) and the bars on either side (0.3° x 3.0°), that remained on the screen for 200 ms. We used degrees of visual angle (º) to express the stimulus size instead of inches or centimeters because it is important to consider the angle between the stimulus lines and the extremities and the eye's lens. We calculated these values assuming a distance of 60cm from the monitor. These same values were also reported in previous studies

with the same task (Menezes et al., 2013). The participant then indicated whether the bars had a similar or different orientation by pressing the “q” or “p” keys on the keyboard, respectively, while a checkerboard pattern was displayed on the screen. Reaction time (RT) and errors were recorded for each trial.

The task was divided into three blocks of different levels of difficulty randomly presented: difficult emotional interference - level 1 (EI_D1), difficult emotional interference – level 2 (EI_D2), and easy emotional interference (EI_E). The orientation of the two bars differed by only 12 ° in the two difficult blocks with some slight difference in orientation at EI_D1 and EI_D2, whereas in the easy block (EI_E), the orientation of the bars differed by 90 °. The task involved two types of images: neutral and emotional/unpleasant. Neutral images portrayed landscapes or objects, while unpleasant images showed mutilated bodies. Forty-two of these images were obtained from the International Affective Picture System (IAPS), while the remaining ones were collected from the Internet (Lang, 2005). The average duration of the task was 20 minutes. We used the E-Prime software, as described by Menezes et al. (2013). Figure 1 depicts an illustration of the Cognitive Discrimination Task. Data on task performance at baseline and endpoint (RT, accuracy) is provided briefly in the Table 1 and Table 2 of the Supplemental Material.

2.4 Statistical analyses

Regression analyses were performed using the variation between baseline and endpoint EI scores for each condition as dependent variables. We included age, gender, and BMI as independent variables in the null models and added treatment group contrasts, HRV, and HRV*Group interaction in the active models. Models were compared using F statistics, and a more inclusive model was considered a superior fit if $p \leq 0.05$. To include BMI as a covariate, since it correlates with HRV (Koenig et al., 2014), we verified that missing data was completely at random using a nonparametric method (Jamshidian & Jalal, 2010), and performed a multiple imputation procedure by chained equations using the MICE package under R (R Core Team, 2019; van Buuren & Groothuis-Oudshoorn, 2011). We used the TestMCARNormality function of the MissMech package for R, which uses a nonparametric approach described by Jamshidian & Jalal 2010, using the Anderson-Darling k-sample test. Reaction time and errors might be considered as indexes of automatic (i.e., bottom-up) sensory reaction and cognitive control, respectively. We calculated Emotional Interference (EI) scores by subtracting the median RT for neutral images from the median RT for emotional images. Positive values indicate emotional

interference on performance. Missing data on the EI data was imputed conservatively using the last observation carried forward (LOCF), but we also reported the results using only the participants that completed all the assessments.

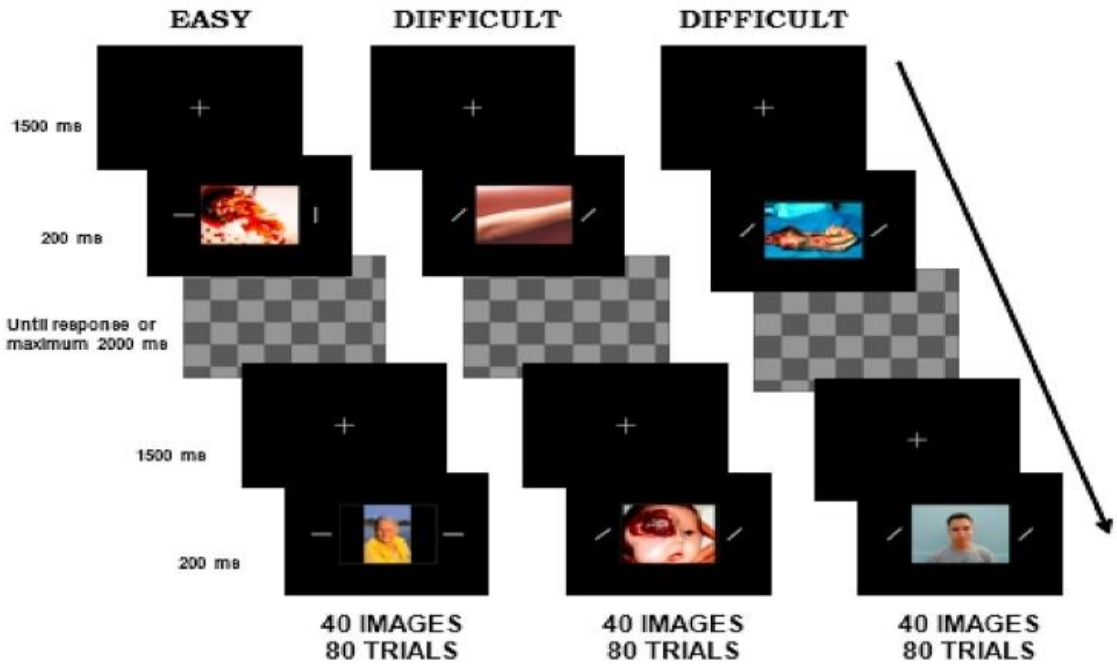

Fig. 1. Cognitive Discrimination Task.

3 RESULTS

3.1 Baseline

The original study randomized 249 individuals. From those, 43 did not attend the first session (8 in BMT, 9 in FLX, and 26 in QoL) and 58 (29 in BMT, 9 in FLX, 20 in QoL) did not complete the interventions. In this present study, forty-two individuals (n=42) were lost due to artifact problems in the HRV signal or because the participant did not attend the HRV assessment (2 BMT, 32 FLX, 8 QoL) and a total of 106 individuals were included. Of those, 45 were randomized to BMT, 31 to FLX, and 30 for the QoL group. Of those, 45 were randomized to BMT, 31 to FLX, and 30 for the QoL group. Participants were mainly female (77.4%; n = 82), and the mean age was 36.64 (±13.4) years old. The majority of the participants had an adequate level of education (94.3% completed high schools at least). The mean HAMA score at baseline was 27.53 (±7.8), the mean PSWQ score was 47.32 (±13,2), and the mean DERS score was 110.35 (±29.3). There was no difference between participants in the BMT and

FLX groups assessed in this study nor in the successive differences between normal heartbeats (RMSSD) assessed in the whole sample. See Table 1 for more details.

Table 1
Baseline Characteristics of Patients.

	BMT (n = 45)	FLX (n = 31)	QoL (n = 30)	p[a]
Female; n (%)	34 (75.5)	23 (74.19)	35 (83.3)	0.89
Age; m(±SD)	37.96 (±15.7)	34.16 (±11.6)		0.256
Education; n (%)				
Completed High School	7 (15.5)	4 (10.8)	10 (33.3)	0.088
Full Higher Education	12 (26.6)	7 (22.6)	6 (20)	
I ncomplete Higher Education	18 (40)	9 (29)	11 (36.7)	
Postgrad/Graduate courses	3 (6.6)	9 (29)	3 (10)	
HAMA; m(±SD)	27.47 (±8.6)	27.43 (±6.8)	27.7 (±7.5)	0.985
PSWQ; m(±SD)	47 (±15.3)	47.5 (±9.2)	47.9 (±11.9)	0.89
DERS; m(±SD)	107.95 (±35.3)	115.1 (±20.2)	110.9 (±23.5)	0.396
Rest RMSSD; m(±SD)	76.37 (±41.2)	62.5 (±31.6)	60.5 (±30.6)	0.295
Baseline EI				
Easy	37.5 (±51.7)	18.0 (±55.9)	36.5 (±60.6)	0.288
Hard 1	34.8 (±89.5)	25.5 (±63.2)	32.1 (±81.2)	0.863
Hard 2	31.7 (±49.7)	21.4 (±84.6)	22.0 (±82.9)	0.753

Notes: BMT: Body in Mind Training Group; DERS: Difficulties in Emotion Regulation Scale; FLX: Fluoxetine Group; HAMA: Hamilton Anxiety Rating Scale; PSWQ: Penn State Worry Questionnaire; QoL: Quality of Life and Psychoeducation Group; RMSSD: root mean square of successive differences between normal heartbeats.

[a] Differences between BMT and FLX estimated through chi-squared test or Fisher's exact test for categorical variables, and through Analysis of Variance (ANOVA) for continuous variables with normal distributions or nonparametric test for independent sample to continuous variables with no normal distribution.

Root mean square of RMSSD change between task and rest conditions was positively correlated with HAMA values. However, there were no significant correlations between RMSSD change with age, baseline DERS or PSWQ, and with changes in the EI during the task at baseline, at endpoint, or during difficult and easy phases of the task. See Table 2 for more details on the Correlation Matrix.

Table 2
RMSSD change correlations.

	r[a]	p value
Baseline Clinical		
Age	0.162	0.162
HAMA	0.278	0.0018[b]
DERS	0.18	0.174
PSWQ	0.009	0.942
Baseline EI		
E	0.100	0.394
D1	−0.022	0.851
D2	0.069	0.555
EI change		
E	0.002	0.984
D1	−0.07	0.551
D2	−0.18	0.122

Notes: DERS: Difficulties in Emotion Regulation Scale; EI_D1: difficult emotional interference at baseline; EI_D2: difficult emotional interference at endpoint; EI_E: easy emotional interference; HAMA: Hamilton Anxiety Rating Scale; PSWQ: Penn State Worry Questionnaire; RMSSD: root mean square of successive differences between normal heartbeats.

[a] Pearson's r (p-value).

[b] $p < 0.05$.

3.2 Main Results

The final multivariate regression model for changing in EI_D2 during the difficult challenges of the task at endpoint considering LOCF included gender, age, imputed BMI, the difference between BMT or FLX and control, and the RMSSD changing from rest to the task at baseline. The association between the RMSSD change from rest to the task at baseline considered two different comparisons: BMT versus control, and FLX versus control. The only predictor in the model was the interaction between RMSSD change from rest to the task and the and FLX versus control (estimated = -80.24; SE = 27.31; p = 0.005). In sum, the HRV change from rest to the task at baseline assessed through RMSDD predicted improvement in EI during difficult challenging at the endpoint in the FLX group. For more details, see Table 3 and Figure 2. Figure 3 depicted RMSSD changes and the reductions in EI in the different treatment groups.

Table 3
Model Coefficients for Difficult Emotional Interference at Endpoint.

					95% Confidence Interval	
Predictor	Estimate	SE	T	P	Lower	Upper
Gender (male – female)	−28.79	18.35	−1.57	0.121	−0.9	0.11
Age	0.44	0.62	0.71	0.482	−0.15	0.30
BMI[a]	2.17	1.74	1.25	0.215	−0.08	0.36
BMT – control	−30.33	19.28	−1.57	0.121	−0.87	0.14
FLX – control	23.90	23.05	1.04	0.304	−0.55	0.59
RMSSD.change	1.65	18.23	0.09	0.928	−0.34	0.37
RMSSD.change * (BMT – control)	14.16	27.44	0.52	0.608	−0.39	0.66
RMSSD.change * (FLX - control)	−80.24	27.31	−2.94	**0.005**	−1.30	−0.25

Notes: BMI: body mass index; BMT: Body in Mind Training Group; FLX: Fluoxetine Group; RMSSD: root mean square of successive differences between normal heartbeats.

[a] Imputed data.

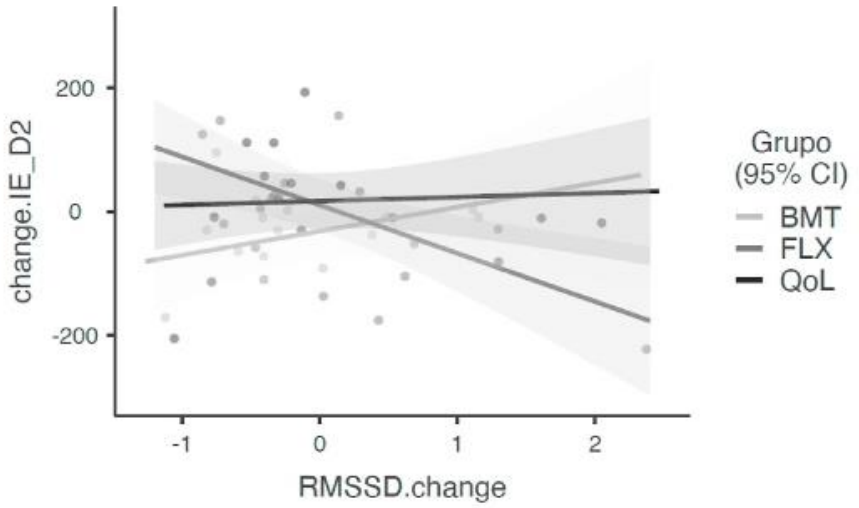

Fig. 2. Correlation between HRV changing from rest to task at baseline (RMSSD.change) and changing in emotional interference during a difficult task at endpoint (change.IE_D2) considering the different intervention groups.

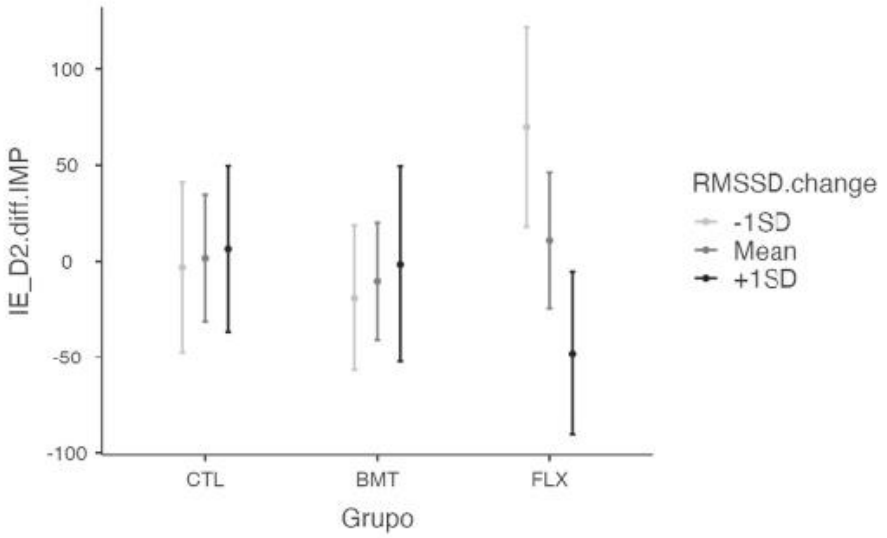

Fig. 3. HRV (RMSSD) changes and the reductions in Emotional Interferenc (EI) in the different treatment groups.
Notes: Control Group (CTL), Body in Mind Training Group (BMT), Fluoxetin Group (FLX).

When the analysis considered only those who completed all assessments, the interaction between RMSSD change from rest to the task, and the FLX versus control remained as a predictor of improvement in EI during difficult challenging at endpoint (estimated = -84.27; SE = 34.44; p = 0.019). In this analysis, the gender was also a predictor (male – female; estimated = -54.14; SE = 26.34; p = 0.047). On the other hand, age (estimated = 0.54; SE = 1.01; p = 0.595), imputed BMI (estimated = 3.29; SE = 2.54; p = 0.203), the difference between BMT (estimated = -62.68; SE = 32.56; p = 0.062) or FLX (estimated = 21.8; SE = 34.34; p = 0.529) and control, the RMSSD change from rest to the task at baseline (estimated = 6.39; SE = 23.75; p = 0.789), and the interaction between the RMSSD change from rest to the task at baseline and BMT versus control (estimated = 32.47; SE = 40.95; p = 0.433) did not predict improvement in EI during difficult challenging at endpoint.

3.3 Secondary Results

The same model was used to predict changes in EI_D1 and EI_E in the task. However, no variable included in the model (gender, age, imputed BMI, the difference between BMT or FLX and control, the RMSSD changing from rest to task at baseline, and the association between the RMSSD changing from rest to task at baseline and BMT versus control or FLX versus control) predicted EI changing at baseline during difficult challenging or during easy challenging. We performed all the analyses considering completers and LOCF.

4 DISCUSSION

In the present study, we investigated the changes of HRV from the rest to the task condition as a predictor of improvement in EI (an objective measure) during a cognitive task with the presentation of neutral and emotional stimuli in patients with GAD. We aimed to verify the effect of different therapeutic interventions (BMT and FLX) compared with the control group under psychophysiological aspects based on this clinical marker. According to our initial hypothesis, the correlation between HRV changing from rest to the task predicted the improvement in EI in the FLX group compared with the control group. However, contrary to our hypothesis, this finding was not reported in the BMT group.

Cognitions and emotions can be influenced by body physiology. Emotion regulation is vital for social functioning (Eisenberg, 2001). During anxiety emotional or physical demands, the sympathetic nervous system becomes more active and produces physiological arousal to assist in adapting to the challenge (Appelhans & Luecken, 2006). Among some adaptations is the modulation of heart rate, which is a measure of the continuous interaction between sympathetic and parasympathetic influences, that showed the capacity to regulate emotional response throughout autonomic flexibility (Christou-Champi et al., 2015; Thayer et al., 2009). Moreover, HRV may be related to emotional dysregulation through its influence on the processing of emotional information. Low HRV is associated with increased negative attention bias and decreased positive attention bias (Armstrong & Olatunji, 2012; Ottaviani et al., 2016). Individuals with low HRV demonstrated greater distraction interference in a task of response inhibition only when the distractors were of the negative valence (Krypotos et al., 2011). The association between low HRV and reduced performance in tasks involving negative emotional stimuli suggests that HRV moderates the effects of distraction from aversive emotional stimuli on attention and emotion regulation (Gillie et al., 2015).

The Polyvagal Theory (Porges, 2007) discusses the anatomical and functional relationships between autonomic functioning and psychopathological anxiety states and behavior. Vagal system dysfunction can lead to inhibition problems, such as cognitive deficits and emotional dysregulation (Beauchaine & Thayer, 2015). Studies reported that patients diagnosed with GAD had an increased heart rate and a decreased HRV (ie, low vagal control) at rest compared to healthy controls, suggesting a basal autonomic state characterized by a decrease in the parasympathetic nervous system (Chang et al., 2019; Kemp et al., 2014; Beauchaine, 2015). In cognitive tests, positive emotions were related to greater parasympathetic

activity, while negative emotions increased sympathetic and decreased vagal activity (Kreibig, Wilhelm, Roth, & Gross; 2007). Another study (Litch et al, 2009) reported that although resting vagal modulation is reduced in patients with anxiety disorders, these reductions were due to antidepressant medications. Therefore, our study is in line with previous data (Chang et al., 2019) showing that higher vagal cardiac reactivity and higher parasympathetic modulation and sympathetic vagal balance would improve emotional regulation.

In our study, we found a correlation between changes in the HRV from rest to the task, and a reduction in EI during the difficult condition in the FLX group only. A previous study has already investigated the relationship between the resting HRV and performance in a task paradigm using images with emotional content in anxious patients. They suggested that lower HRV at rest was associated with deficits in positive content processing and with increased attention to images with negative aspects (Grol & De Raedt, 2020). Krypotos et al. (2011) carried out a study investigating HRV and cognitive task with negative and neutral valence images. They found that individuals with low HRV took a longer time to inhibit responses than those with high HRV, indicating that HRV could impact the effectiveness of responses after a negative stimulus. People with low HRV interpret mild stimuli as threatening, causing body significant stress (Krypotos et al., 2011; Park et al., 2014). The results of our study corroborate with the understanding that the failure in the cognitive processing of emotional stimulation is associated with individuals with low HRV and that some interventions, such as drug treatment, can contribute to attentional control and improved emotional regulation (Capitão et al., 2015; Cassano et al., 2002).

However, we did not find the same results in the BMT group, contradicting our hypothesis and previous studies that suggested the effects of mindfulness approaches on emotional regulation. Mindfulness training can help to reduce reactivity and faster recover from negative emotional states, and from aversive stimuli (Crosswell et al., 2017; Keng et al., 2011). Maybe, our results are not in agreement with the mindfulness literature because participants from the FLX group had greater symptomatic improvement according to HAMA rating scores than the BMT group (Costa et al., 2020). Our study has some limitations. First, we measured HRV in different times depending on the participants' availability to come to the hospital ranging from morning to afternoon. Moreover, we lost some HRV measures due to problems in the artifacts and interference in the data processing. However, the results from LOCF and completer analysis are very similar. Second, we calculated the sample size based on the clinical outcomes of the efficacy randomized controlled trial and not on this research purpose. Albeit our hypothesis was constructed a priori, a type II error can occur when we claim that we did

not find a significant relationship between changes in baseline HRV and improvement in IE in the BMT group. Third, we did not control our analysis for important clinical variables as cardiovascular conditions and tobacco use. However, we used a random sample that aims to eliminate confounding factors between groups, and our sample was mainly composed of healthy and young participants. Finally, we did not find a correlation between clinical improvement (assessed throughout mean difference in HAMA from the endpoint to baseline) and EI_D2 (Pearson correlation = -0.11; $p = 0.354$). However, the improvement in the cognitive process can occur due to different mechanisms besides the improvement of clinical symptoms. In addition, the HAMA scale might not capture the improvement in EI. On the other hand, changes in HRV can predict improvement only in the FLX group, which was the group with the highest clinical response rates (Costa et al., 2020). Previous studies suggested that fluoxetine can modulate emotional processing and improve cognitive performance (Capitão et al., 2015; Cassano et al., 2002; Marwari & Dawe, 2018), which is consistent with our findings.

Our study has some important strengths. First, we used a gold-standard design (randomized clinical trial) to assess objective and easily measurable measures in psychological science. Second, our results brought important finding considering HRV as a promising predictor of response to an antidepressant in GAD, helping with the development of more personalized treatment. Finally, this study corroborates with the literature in order to better comprehend the relationship between cognitions, emotions, and physiology. Therefore, HRV and EI assessed through cognitive task are research tools for assessing the GAD mechanisms, and, maybe, future relevant tools to investigate GAD in clinical practices.

In summary, we found that the baseline HRV changing from rest to task predicted improvement in EI in the FLX group, which is in agreement with our hypothesis, but not in the BMT group. This finding is clinically relevant since it may help us to develop more effective and personalized interventions for GAD. Moreover, the use of behavioral and physiological measures in the processing of emotional information enabled a wider view of the relationship between HRV and emotional regulation in patients with GAD, offering subsidies for future research that investigates the understanding of transdiagnostic bio-behavioral constructs relevant to mental health. Future studies may explore how mindfulness training can be designed to improve specific components of emotional regulation in anxious patients.

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REFERENCES

Agelink, M. W., Boz, C., Ullrich, H., & Andrich, J., 2002. Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment. *Psychiatry Research*, *113*(1–2), 139–149.

Amorim, Patrícia. 2000., "Mini International Neuropsychiatric Interview (MINI): Validation of a Short Structured Diagnostic Psychiatric Interview." *Brazilian Journal of Psychiatry* 22(3):106–15. doi: 10.1590/S1516-44462000000300003.

Appelhans, B. M., & Luecken, L. J., 2006. Heart Rate Variability as an Index of Regulated Emotional Responding. *Review of General Psychology*, *10*(3), 229–240. https://doi.org/10.1037/1089-2680.10.3.229.

Armstrong, T., & Olatunji, B. O., 2012. Eye tracking of attention in the affective disorders: A meta-analytic review and synthesis. *Clinical Psychology Review*, *32*(8), 704–723. https://doi.org/10.1016/j.cpr.2012.09.004.

Azevedo, T. M., Volchan, E., Imbiriba, L. A., Rodrigues, E. C., Oliveira, J. M., Oliveira, L. F., Lutterbach, L. G., & Vargas, C. D., 2005. A freezing-like posture to pictures of mutilation. *Psychophysiology*, *42*(3), 255–260. https://doi.org/10.1111/j.1469-8986.2005.00287.

Ball, S., Marangell, L. B., Lipsius, S., & Russell, J. M., 2013. Brain-derived neurotrophic factor in generalized anxiety disorder: Results from a duloxetine clinical trial. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *43*, 217–221. https://doi.org/10.1016/j.pnpbp.2013.01.002.

Beauchaine, Theodore P., and Julian F. Thayer., 2015. "Heart Rate Variability as a Transdiagnostic Biomarker of Psychopathology." *International Journal of Psychophysiology* 98(2):338–50. doi: 10.1016/j.ijpsycho.2015.08.004.

Capitão, L. P., Murphy, S. E., Browning, M., Cowen, P. J., & Harmer, C. J., 2015. Acute fluoxetine modulates emotional processing in young adult volunteers. *Psychological Medicine*, *45*(11), 2295–2308. https://doi.org/10.1017/S0033291715000240.

Cassano, G. B., Puca, F., Scapicchio, P. L., Trabucchi, M., & Italian Study Group on Depression in Elderly Patients., 2002. Paroxetine and fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. *The Journal of Clinical Psychiatry*, *63*(5), 396–402.

Castillo, Cristian, Leonardo Macrini, Elie Cheniaux, and Jesús Landeira-Fernandez., 2010. "Psychometric Properties and Latent Structure of the Portuguese Version of the Penn State Worry Questionnaire." *The Spanish Journal of Psychology* 13(1):431–43.

Chalmers, J. A., Quintana, D. S., Abbott, M. J.-A., & Kemp, A. H., 2014. Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. *Frontiers in Psychiatry*, *5*, 80. https://doi.org/10.3389/fpsyt.2014.00080.

Chang, H.-A., Fang, W.-H., Wan, F.-J., Tzeng, N.-S., Liu, Y.-P., Shyu, J.-F., Chang, T.-C., Huang, S.-Y., & Chang, C.-C., 2019. Attenuated vagally-mediated heart rate variability at rest and in response to postural maneuvers in patients with generalized anxiety disorder. *Psychological Medicine*, 1–9. https://doi.org/10.1017/S0033291719001302.

Christou-Champi, S., Farrow, T. F. D., & Webb, T. L,. 2015. Automatic control of negative emotions: Evidence that structured practice increases the efficiency of emotion regulation. *Cognition and Emotion*, *29*(2), 319–331. https://doi.org/10.1080/02699931.2014.901213.

Coutinho, Joana, Eugénia Ribeiro, Raquel Ferreirinha, and Paulo Dias., 2010. "The Portuguese Version of the Difficulties in Emotion Regulation Scale and Its Relationship with Psychopathological Symptoms." *Archives of Clinical Psychiatry (São Paulo)* 37(4):145–51. doi: 10.1590/S0101-60832010000400001.

Crosswell, A. D., Moreno, P. I., Raposa, E. B., Motivala, S. J., Stanton, A. L., Ganz, P. A., & Bower, J. E. 2017., Effects of mindfulness training on emotional and physiologic recovery from induced negative affect. *Psychoneuroendocrinology*, *86*, 78–86. https://doi.org/10.1016/j.psyneuen.2017.08.003.

Cuthbert, B., & Insel, T., 2010. The Data of Diagnosis: New Approaches to Psychiatric Classification. *Psychiatry: Interpersonal and Biological Processes*, *73*(4), 311–314. https://doi.org/10.1521/psyc.2010.73.4.311.

Dekker, J. M., Schouten, E. G., Klootwijk, P., Pool, J., Swenne, C. A., & Kromhout, D., 1997. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. *American Journal of Epidemiology*, *145*(10), 899–908. https://doi.org/10.1093/oxfordjournals.aje.a009049.

Eisenberg, N. 2001., The Core and Correlates of Affective Social Competence. *Social Development*, *10*(1), 120–124. https://doi.org/10.1111/1467-9507.00151.

Electrophysiology, Task Force of the European Society., 1996. "Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use." *Circulation* 93(5):1043–65. doi: 10.1161/01.CIR.93.5.1043.

Erthal, F. S., De Oliveira, L., Mocaiber, I., Pereira, M. G., Machado-Pinheiro, W., Volchan, E., & Pessoa, L., 2005. Load-dependent modulation of affective picture processing. Cognitive, Affective, & Behavioral Neuroscience, 5(4), 388–395. https://doi.org/10.3758/CABN.5.4.388.

Geisler, F. C. M., Vennewald, N., Kubiak, T., & Weber, H., 2010. The impact of heart rate variability on subjective well-being is mediated by emotion regulation. Personality and Individual Differences, 49(7), 723–728. https://doi.org/10.1016/j.paid.2010.06.015.

Gillie, B. L., Vasey, M. W., & Thayer, J. F., 2015. Individual differences in resting heart rate variability moderate thought suppression success: HRV and thought suppression. Psychophysiology, 52(9), 1149–1160. https://doi.org/10.1111/psyp.12443.

Gratz, Kim L., and Lizabeth Roemer., 2004. "Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale." *Journal of Psychopathology and Behavioral Assessment* 26(1):41–54. doi: 10.1023/B:JOBA.0000007455.08539.94.

Grol, M., & De Raedt, R., 2020. The link between resting heart rate variability and affective flexibility. Cognitive, Affective, & Behavioral Neuroscience, 20(4), 746–756. https://doi.org/10.3758/s13415-020-00800-w.

Hamilton, M., 1959. "The Assessment of Anxiety States by Rating." *The British Journal of Medical Psychology* 32(1):50–55.

Jamshidian, M., & Jalal, S., 2010. Tests of homoscedasticity, normality, and missing completely at random for incomplete multivariate data. Psychometrika. https://doi.org/10.1007/s11336-010-9175-3.

Kemp, A. H., Brunoni, A. R., Santos, I. S., Nunes, M. A., Dantas, E. M., Carvalho de Figueiredo, R., Pereira, A. C., Ribeiro, A. L. P., Mill, J. G., Andreão, R. V., Thayer, J. F., Benseñor, I. M., & Lotufo, P. A., 2014. Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability: An ELSA-Brasil cohort baseline study. The American Journal of Psychiatry, 171(12), 1328–1334. https://doi.org/10.1176/appi.ajp.2014.13121605.

Keng, S.-L., Smoski, M. J., & Robins, C. J., 2011. Effects of mindfulness on psychological health: A review of empirical studies. Clinical Psychology Review, 31(6), 1041–1056. https://doi.org/10.1016/j.cpr.2011.04.006.

Koenig, J., M. N. Jarczok, M. Warth, R. J. Ellis, C. Bach, T. K. Hillecke, and J. F. Thayer., 2014. "Body Mass Index Is Related to Autonomic Nervous System Activity as Measured by Heart Rate Variability--a Replication Using Short Term Measurements." *The Journal of Nutrition, Health & Aging* 18(3):300–302. doi: 10.1007/s12603-014-0022-6.

Kreibig, Sylvia D., Frank H. Wilhelm, Walton T. Roth, and James J. Gross., 2007. "Cardiovascular, Electrodermal, and Respiratory Response Patterns to Fear- and Sadness-Inducing Films." *Psychophysiology* 44(5):787–806. doi: 10.1111/j.1469-8986.2007.00550.x.

Krypotos, A.-M., Jahfari, S., van Ast, V. A., Kindt, M., & Forstmann, B. U., 2011. Individual Differences in Heart Rate Variability Predict the Degree of Slowing during Response Inhibition and Initiation in the Presence of Emotional Stimuli. Frontiers in Psychology, 2. https://doi.org/10.3389/fpsyg.2011.00278.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N., 2005. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Technical Report A-6, Gainesville, FL: University of Florida. 749.

Levine, J. C., Fleming, R., Piedmont, J. I., Cain, S. M., & Chen, W.-J., 2016. Heart rate variability and generalized anxiety disorder during laboratory-induced worry and aversive

imagery. Journal of Affective Disorders, 205, 207–215. https://doi.org/10.1016/j.jad.2016.07.019.

Licht, Carmilla M. M., Eco J. C. de Geus, Richard van Dyck, and Brenda W. J. H. Penninx., 2009. "Association between Anxiety Disorders and Heart Rate Variability in The Netherlands Study of Depression and Anxiety (NESDA):" *Psychosomatic Medicine* 71(5):508–18. doi: 10.1097/PSY.0b013e3181a292a6.

Marwari, S., & Dawe, G. S., 2018. (R)-fluoxetine enhances cognitive flexibility and hippocampal cell proliferation in mice. Journal of Psychopharmacology, 32(4), 441–457. https://doi.org/10.1177/0269881118754733.

McCraty, R., & Shaffer, F., 2015. Heart Rate Variability: New Perspectives on Physiological Mechanisms, Assessment of Self-regulatory Capacity, and Health risk. Global Advances in Health and Medicine, 4(1), 46–61. https://doi.org/10.7453/gahmj.2014.073.

Menezes, C. B., de Paula Couto, M. C., Buratto, L. G., Erthal, F., Pereira, M. G., & Bizarro, L., 2013. The Improvement of Emotion and Attention Regulation after a 6-Week Training of Focused Meditation: A Randomized Controlled Trial. Evidence-Based Complementary and Alternative Medicine, 2013, 1–11. https://doi.org/10.1155/2013/984678.

Mennin, D. S., & Fresco, D. M., 2013. What, Me Worry and Ruminate About DSM-5 and RDoC? The Importance of Targeting Negative Self-Referential Processing. Clinical Psychology: Science and Practice, 20(3), 258–267. https://doi.org/10.1111/cpsp.12038.

Meyer, T. J., M. L. Miller, R. L. Metzger, and T. D. Borkovec., 1990. "Development and Validation of the Penn State Worry Questionnaire." *Behaviour Research and Therapy* 28(6):487–95.

Moreno, André Luiz, Diogo Araújo DeSousa, Ana Maria Frota Lisbôa Pereira de Souza, Gisele Gus Manfro, Giovanni Abrahão Salum, Silvia Helena Koller, Flávia de Lima Osório, and José Alexandre de Souza Crippa., 2016. "Factor Structure, Reliability, and Item Parameters of the Brazilian-Portuguese Version of the GAD-7 Questionnaire." *Temas Em Psicologia* 24(1):367–76. doi: 10.9788/TP2016.1-25.

Newman, M. G., & Llera, S. J., 2011. A novel theory of experiential avoidance in generalized anxiety disorder: A review and synthesis of research supporting a contrast avoidance model of worry. Clinical Psychology Review, 31(3), 371–382. https://doi.org/10.1016/j.cpr.2011.01.008.

Newman, M. G., Llera, S. J., Erickson, T. M., Przeworski, A., & Castonguay, L. G., 2013. Worry and generalized anxiety disorder: A review and theoretical synthesis of evidence on nature, etiology, mechanisms, and treatment. Annual Review of Clinical Psychology, 9, 275–297. https://doi.org/10.1146/annurev-clinpsy-050212-185544.

Ottaviani, C., Thayer, J. F., Verkuil, B., Lonigro, A., Medea, B., Couyoumdjian, A., & Brosschot, J. F., 2016. Physiological concomitants of perseverative cognition: A systematic review and meta-analysis. Psychological Bulletin, 142(3), 231–259. https://doi.org/10.1037/bul0000036

Park, G., Vasey, M. W., Van Bavel, J. J., & Thayer, J. F., 2014. When tonic cardiac vagal tone predicts changes in phasic vagal tone: The role of fear and perceptual load: Tonic and

phasic cardiac activity under load. Psychophysiology, 51(5), 419–426. https://doi.org/10.1111/psyp.12186.

Porges, Stephen W., 2007. “The Polyvagal Perspective.” *Biological Psychology* 74(2):116–43. doi: 10.1016/j.biopsycho.2006.06.009.

R Core Tem. 2019., R: A language and environment for statistical computing. In R Foundation for Statistical Computing.

Russell T.A., & Tatton-Ramons T., 2014. Body in mind training: Mindful movement for the clinical setting. Neuro-Disability & Psychotherapy. 108–136.

Russell, T. (2011). Body in mind training: Mindful movement for severe and enduring mental illness. British Journal of Wellbeing, 2(4), 13–16. https://doi.org/10.12968/bjow.2011.2.4.13.

Shah, A. J., Lampert, R., Goldberg, J., Veledar, E., Bremner, J. D., & Vaccarino, V., 2013. Posttraumatic stress disorder and impaired autonomic modulation in male twins. Biological Psychiatry, 73(11), 1103–1110. https://doi.org/10.1016/j.biopsych.2013.01.019

Sheehan, D. V., Y. Lecrubier, K. H. Sheehan, P. Amorim, J. Janavs, E. Weiller, T. Hergueta, R. Baker, and G. C. Dunbar., 1998. “The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10.” *The Journal of Clinical Psychiatry* 59 Suppl 20:22-33;quiz 34-57.

Shinba, Toshikazu, Nobutoshi Kariya, Yasue Matsui, Nobuyuki Ozawa, Yoshiki Matsuda, and Ken-ichi Yamamoto., 2008. “Decrease in Heart Rate Variability Response to Task Is Related to Anxiety and Depressiveness in Normal Subjects: Heart Rate Variability Responsiveness.” *Psychiatry and Clinical Neurosciences* 62(5):603–9. doi: 10.1111/j.1440-1819.2008.01855.x.

Shu, L., Xie, J., Yang, M., Li, Z., Li, Z., Liao, D., Xu, X., & Yang, X., 2018. A Review of Emotion Recognition Using Physiological Signals. Sensors, 18(7), 2074. https://doi.org/10.3390/s18072074.

Spitzer, Robert L., Kurt Kroenke, Janet B. W. Williams, and Bernd Löwe., 2006. “A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7.” *Archives of Internal Medicine* 166(10):1092–97. doi: 10.1001/archinte.166.10.1092.

Steinfurth, E. C. K., Wendt, J., Geisler, F., Hamm, A. O., Thayer, J. F., & Koenig, J., 2018. Resting State Vagally-Mediated Heart Rate Variability Is Associated With Neural Activity During Explicit Emotion Regulation. Frontiers in Neuroscience, 12, 794. https://doi.org/10.3389/fnins.2018.00794.

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H., 2009. Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health. Annals of Behavioral Medicine, 37(2), 141–153. https://doi.org/10.1007/s12160-009-9101-z.

Van Buuren, S., & Groothuis-Oudshoorn, K., 2011. Mice: Multivariate imputation by chained equations in R. Journal of Statistical Software. https://doi.org/10.18637/jss.v045.i03.

Vest, A. N., Da Poian, G., Li, Q., Liu, C., Nemati, S., Shah, A. J., & Clifford, G. D., 2018. An open source benchmarked toolbox for cardiovascular waveform and interval analysis. Physiological Measurement, 39(10), 105004. https://doi.org/10.1088/1361-6579/aae021.

14.2 Artigo 2

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Effects of Different Treatments for Generalized Anxiety Disorder on Reactivity to Aversive Stimuli and Emotional Interference: a Randomized Clinical Trial

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Abstract

Introduction: Anxiety and its cognitive component — worry — are associated with impairments in several cognitive processes. Cognitive control plays a role in symptom maintenance in patients with Generalized Anxiety Disorders (GAD). **Objective:** to investigate the association between cognitive control and emotional interference in patients with GAD and evaluate the effects of different treatment modalities on these processes. **Method:** We assessed the cognitive performance of GAD adult patients using a discrimination task at baseline and after an 8-week randomized controlled trial assessing a mindfulness-based intervention (BMT), fluoxetine

(FLX), and an active group (QoL). Data were analyzed using mixed ANOVA and Bonferroni-corrected post hoc tests. **Results:** A total of 216 participants completed the intervention and cognitive assessments (n= 69 in FLX group, n= 73 in BMT group, and n= 74 in QoL). The BMT group showed a significant increase in accuracy for trials involving emotional stimuli from baseline to post-treatment; however, the FLX group was the only one to demonstrate a significant reduction in emotional interference. Furthermore, participants from the FLX and QoL groups improved reaction time and attentional processing in the cognitive task. **Conclusions:** These findings showed that all three interventions might affect information processing and reactivity to emotional stimuli through different mechanisms.

Keywords: Generalized anxiety disorder (GAD); attentional control; emotional control; cognitive tasks.

Effects of Different Treatments for Generalized Anxiety Disorder on Reactivity to Aversive Stimuli and Emotional Interference: a Randomized Clinical Trial

Introduction

Generalized anxiety disorder (GAD) is characterized by persistent and excessive anxiety and worry, which are difficult to control and persist for at least 6 months (1). The 12-month prevalence of GAD is 3.1% (2,3) and the physical and psychological symptoms associated with this disorder cause significant distress and functional impairment.

Anxiety and its cognitive component — worry — are associated with reduced performance in several cognitive domains, including attention. Patients with GAD enhance threat detection increasing the perception of danger(3,4). Moreover, they impair attention regulation and create a constant need for cognitive strategies to compensate for emotion regulation difficulties leading to rumination and excessive worry (5–7). The cognitive model of GAD posits that impairments in cognitive or attentional control, which orient attention and facilitate goal-seeking behaviors, may play an important role in maintaining the symptoms of anxiety as well as the disorder itself (8,9). Some studies evaluated participants with high anxiety using the Stroop test and reported that they are biased toward threat-related stimuli and showed significant attentional impairments (10–12). In addition to attentional bias, worry can also be associated with impairments in response inhibition, characterized by the ability to voluntarily suppress automatic responses, in the attentional tasks and memory (11,13). Individuals with higher levels of worry and with GAD show impairments in inhibition process in comparison with a control group evaluated with several tasks as the Stroop test, the go/no-go, and the flanker

task (8,14,15). Additionally, a longitudinal study found that impairments in global cognition and executive functioning may constitute risk factors for GAD nearly a decade later (16).

A study suggested that attentional control training can modify the attention bias, which, in turn, influences cognitive reassessment to decrease negative emotions (17).

Given the prominence of impairments in attention and emotion regulation in GAD, these processes are often affected by treatments for this disorder. A previous study of patients with GAD suggested that selective serotonin reuptake inhibitors (SSRIs) improved executive function and memory (18) corroborating the notion that antidepressants, in general, can improve cognitive function and modulate emotional processing (19,20). While attentional control is not directly targeted by cognitive-behavioral therapy (CBT), studies have found that patients with GAD show improved cognitive control over threat-related distractors after cognitive restructuring (21,22). In a large randomized clinical trial comparing mindfulness and attention control in the treatment of GAD, Hoge et al., (2013) (23), found that participants who completed a mindfulness-based cognitive therapy (MBCT) program showed reduced stress reactivity during a cognitive task. Other studies have also reported reductions in anxiety and improvements in attention and emotion regulation after mindfulness training in patients with GAD (24–26). However, no investigations to date have compared the effects of different treatments on attentional and emotional processes in patients with anxiety.

The aim of this study was therefore to investigate the association between cognitive control and emotional interference according to a cognitive task in patients with GAD from a randomized control trial with three treatment arms: medication (fluoxetine; FLX), *mindfulness* (body in mind training; BMT) and an active control treatment (quality of life and psychoeducation; QoL). Our goal was to investigate the effects of each treatment on emotional processing. We hypothesized that, due to BMT effects on emotion regulation, participants who completed this treatment modality would have better emotion regulation than the other groups. This would be reflected by a reduction in emotional interference and faster response times in a post-intervention cognitive assessment. It was also hypothesized that FLX would affect cognitive processing and increase attentional control.

Materials and Methods

Design

This study is a single-blinded parallel three-arm randomized clinical trial. Patients were evaluated prior to randomization (baseline), at week 5 and at the end of the treatment (week 8). The trial was registered at ClinicalTrials.gov (NCT03072264) and all participants gave their

written informed consent before entering the study (Ethics Committee of Hospital de Clínicas de Porto Alegre, number 20160301).

Participants

We recruited the participants from the community through media advertisement, inviting individuals with GAD symptoms to participate in this study. Inclusion criteria consisted of age over 18 years, a primary diagnosis of GAD according to the M.I.N.I., and the ability to make weekly visits to the Hospital de Clinicas de Porto Alegre for a period of 8 weeks. For further information on sample selection please see Costa et al (2020) (27).

Procedures

Trained psychologists and psychiatrists evaluated all participants. After initial telephone screening, potential participants underwent a structured diagnostic clinical interview - Mini-International Neuropsychiatric Interview (M.I.N.I.) and completed the instruments and measures described in the following section. Participants also completed self-administered questionnaires and a cognitive task before and after the intervention to evaluate clinical and cognitive variables. Data collection and interventions were performed at Hospital de Clínicas de Porto Alegre (HCPA) in the south of Brazil.

Treatment Conditions

Experimental Group

Body in Mind Training (BMT)

This mindfulness-based protocol was developed by a researcher from the King's College (28). The intervention was designed for groups of 10-15 participants, who are trained to practice mindfulness through physical movements that encourage focus and promote attentional, emotional, and proprioceptive self-regulation, in addition to self-compassion. These practices were trained over 8 weekly sessions, with a duration of 120 minutes each. The group was led by a researcher trained in the BMT method. For further details, see Costa et al (2020) (27).

Fluoxetine Group (FLX)

The FLX group received pharmacological treatment, starting with 20 mg fluoxetine in week 1, and if necessary, increasing to 40 mg in week 3 depending on response and tolerability. Patients had weekly follow-up visits with a psychiatrist through all 8 weeks of the study (article). For further details, see Costa et al (2020) (27).

Quality of Life Group (QoL)

The active control group attended 8 weekly sessions led by a psychologist with experience in group therapy. Sessions lasted approximately 120 minutes each. The intervention involved 10-15 participants and consisted of psychoeducation and the discussion of changes in lifestyle habits that may help manage anxiety. See Costa et al (2020) (27), for further details. The active control group and the mindfulness-based protocol had homework with activities related to each meeting.

Instruments

Primary outcomes

Cognitive Discrimination Task

This instrument was developed to evaluate the effect of aversive images on performance in a simple stimulus discrimination task (29,30). In each trial, a neutral or aversive image was presented in the center of a computer screen, flanked by two bars with different orientations. Participants were instructed to ignore the images and simply indicate, as quickly as possible, whether or not the bars were oriented in the same direction. The task began with a training trial, followed by three blocks of images (Figure 1).

In each trial, a fixation cross was shown at the center of the screen for 1500 ms, followed by the central image (size: 9° x 12°) and the bars on either side (0.3° x 3.0°), which remained on the screen for 200 ms. The participant then indicated whether the bars had a similar or different orientation by pressing the “q” or “p” keys on the keyboard, respectively, while a checkerboard pattern was displayed on the screen. Reaction time (RT) and errors were recorded for each trial. The task was divided into three blocks of different levels of difficulty. In the two difficult blocks, the orientation of the two bars differed by only 12°, while in the easy block, the orientation of the bars differed by 90°. The task involved two types of images: neutral and emotional/unpleasant. Neutral images portrayed landscapes or objects, while unpleasant images showed mutilated bodies. Sixty images of each type were used, for a total of 120. Forty-two of these were obtained from the International Affective Picture System (IAPS) while the

remaining images were collected from the Internet (31). The average duration of the task was 20 minutes. We used the E-Prime software as described by Menezes et al. (2013)(30).

Secundary outcomes

Mini-International Neuropsychiatric Interview (M.I.N.I.)

The M.I.N.I is a structured and validated interview schedule for the diagnosis of psychiatric illnesses according to DSM-IV and ICD-10 criteria (25). It has been translated, adapted and validated for use in the Brazilian population. In the present study, the researchers adapted the instrument to include DSM-5 criteria.

Hamilton Anxiety Rating Scale (HAM-A)

This 14-item scale is a widely used and validated measure of anxiety symptom severity (32,33) Its validity and reliability in the Brazilian population have been established in previous studies (34).

Hamilton Depression Rating Scale (HAM-D)

This 21-item scale is considered the gold-standard for the assessment of depressive symptom severity (35,36). The Brazilian version of the instrument has demonstrated high reliability and clear evidence of discriminant and convergent validity (35,37).

WHOQOL-Bref

This measure of quality of life contains 26 items divided into 4 domains: physical, psychological, social relationships and environment. The WHOQOL-Bref has demonstrated good internal consistency; discriminant, concurrent and content validity; and test-retest reliability in the Brazilian population (38).

Difficulties in Emotion Regulation Scale (DERS)

This instrument evaluates emotion regulation in 6 domains: non-acceptance of negative emotions; inability to engage in goal-directed behaviors when distressed; difficulty regulating behavior when experiencing negative emotions; limited access to effective emotion regulation strategies; lack of emotional awareness; lack of emotional clarity. The Brazilian version of the DERS has demonstrated adequate internal consistency (39).

Penn State Worry Questionnaire (PSWQ)

This is a self-administered measure of worry (40,41). containing 16 items scored on a 1 to 5 Likert scale; the scale evaluates the presence of generalized, excessive and uncontrollable worry, and has demonstrated the ability to identify individuals with GAD .Previous studies support the internal consistency of the Portuguese-language version of the PSWQ (42).

Randomization and masking

Participants were randomly allocated in a ratio 1:1:1 to receive one of the three interventions: BMT, QoL or FLX. The randomization was performed through sealed and opaque envelopes. The assessments were performed by blinded evaluators at the 5th and at the end of the intervention. The evaluators were researchers from the research group because of the nature of the intervention, neither therapists nor participants could be masked. However, participants were not aware about the experimental/control groups. Also, they were instructed not to talk about the intervention to the blinded evaluators.

Primary and secondary outcomes

The primary outcome (adjusted for potential confounders) is the clinical efficacy of treatment in control attention and control emotion that was assessed by Discrimination Task at baseline and in the end of the treatment (week 8). Secondary outcome measures included the evaluation of HAM-A, HAM-D, WHOQOL, DERS, PSQW. All outcome measures were evaluated at baseline, at week 5, and at the end of treatment (week 8).

Statistical Analysis

The association between baseline variables for the total sample was assessed using Pearson correlations.

Group differences on the discrimination task were examined using a series of mixed ANCOVAs, controlling for within-group effects of time (pre- and post-treatment), task conditions (D1, D2 and E) and type of stimulus displayed (emotional or neutral). Sex was included as a covariate in all analyses. We used Bonferroni corrected post-hoc tests to control for multiple comparisons. All analyses were conducted using the Statistical Package for Social Sciences (SPSS), version 22. Results were considered significant at $p < 0.05$, and effect sizes were reported for all analyses.

Results

Sample Characteristics

Patients were recruited and included from January 2017 to August 2018 in four waves (approximately one wave of around 60 participants each semester). The first wave of participants started treatment in March 2017 and the last one ended treatment in December 2018. A total of 342 individuals were selected to undergo clinical evaluation after the first phone call screen (that assessed 1109 individuals). After the clinical interview, we included 249 participants. Of those, 84 were randomized to BMT, 81 to FLX, and 84 to QoL. At baseline, 242 participants underwent cognitive testing. Considering the power of 90%, a significance level of 0.05, using the article as reference (Menezes et al., 2013), the estimate of the sample calculation was n = (162) , that is (54 per group). WINPEPI V11.43 was used. However, we excluded the scores of 26 individuals due to task learning difficulties (e.g., errors in all blocks of the task or reaction time recording errors). The final sample at baseline consisted of 216 participants (73 in the BMT group; 69 in the FLX group; 74 in the QoL group) with a mean age of 35.15 (SD, 13.044) years. We reported only one severe adverse effect (hypomanic symptoms in FLX).

Participant characteristics at baseline, including age and psychometric test scores, are depicted in Table 1. No age differences were observed between treatment groups ($F[2, 213] = 1.356$, $p = 0.260$, partial $\eta^2 = 0.013$). Similarly, the groups did not differ with regard to gender distribution ($\chi^2[2, N=216] = 0.787$, $p = 0.675$, Cramer's $V = 0.60$) or education levels ($\chi^2[2, N = 213] = 1.866$, $p = 0.393$, Cramer's $V = 0.94$). Between-group differences in clinical self-report measures were analyzed using MANOVA due to the high correlations between variables. No between-group differences in these instruments were observed at baseline ($F[10, 324] = 0.605$, $p = 0.600$, partial $\eta^2 = 0.025$, Wilks' $\lambda = 0.951$).

We evaluated baseline differences in performance between men and women on the discrimination task using ANCOVA. No interaction was observed between sex and emotional interference (EI) ($F[1,894, 428] = 0.305$, $p = 0.725$, partial $\eta^2 = 0.001$). Both men and women responded more slowly to emotional ($M = 733.77$, $SEM = 15.32$) relative to neutral stimuli ($M = 710.05$, $SEM = 14.31$). However, a significant interaction between sex and accuracy for each type of stimulus showed that men ($M = 27.52$, $SEM = 0.465$) were more accurate than women in trials with neutral stimuli ($M = 25.98$, $SEM = 0.240$) ($p = 0.003$).

Pearson correlations did not reveal significant associations between clinical self-report measures and EI in the discrimination task either at baseline or after treatment (all p values > 0.057). These findings suggest that psychiatric symptom severity and quality of life were not associated with performance on the cognitive task.

Treatment Effects

We screened the items for extreme values before comparing the performance on the *discrimination task* between treatment groups. As in the study by Menezes et al. (2013) (30), we excluded RTs below 200 ms or above 2000 ms from analysis, and median values were used to represent central tendency. We excluded 867 responses (1.47% of total responses) from the baseline analysis and 529 from the post-treatment assessment (1.62% of total responses). The EI index was calculated by subtracting the RT for trials with neutral images from that of trials with emotional stimuli (RTEmotional - RTNeutral). Positive scores on this measure were indicative of interference from emotional images on participant responses. We used the RT for each image as a measure of reactivity. We also analyzed participant accuracy. A total of 19,404 errors were observed at baseline (32.9%) and 10,930 in the post-intervention assessment (33.6%). We assessed the effect of treatment on EI using a 3 (BMT, FLX, QoL) x 2 (pre- and post-treatment) x 3 (D1, D2, and D3) ANOVA, with sex as a covariate. A significant interaction was observed between treatment group and EI ($F[2, 129] = 3.222$, $p = 0.043$, partial $\eta^2 = 0.048$). This interaction is depicted in Figure 1. Bonferroni post-hoc tests revealed that EI was only affected by medication ($p = 0.001$), with the FLX group showing a significant reduction in scores from baseline ($M = 39.23$, $SEM = 7.868$) to post-treatment ($M = 11.52$, $SEM = 5.884$).

We measured the effect of treatment on stimulus reactivity in the discrimination task using RTs to neutral and emotional trials. These values were compared between groups, time points, and trial blocks using ANCOVA. Descriptive data for participant RTs are shown in Table 2. Again, we observed a significant effect of time ($F[1, 130] = 24.769$, $p < 0.001$, partial $\eta^2 = 0.160$), with RTs decreasing from baseline ($M = 729.90$, $SEM = 13.730$) to post-treatment ($M = 664.91$, $SEM = 10.807$), demonstrating the expected habituation effect. The interaction between treatment, time and condition did not significantly affect the RT for each stimulus ($F[4, 260] = 0.268$, $p = 0.878$, partial $\eta^2 = 0.004$). However, the exclusion of condition from the analysis revealed a significant interaction between treatment, time and stimulus type ($F[2, 130] = 3.219$, $p = 0.043$, partial $\eta^2 = 0.047$). Post-hoc tests showed that the FLX and QoL groups showed significant reductions in RT for both neutral and emotional stimuli (Figure 3).

We assessed the changes in accuracy for trials containing neutral and emotional stimuli from pre- to post-treatment using a mixed ANCOVA comparing the effects of each treatment on the number of correct answers for emotional and neutral trials on each block of the discrimination task. Accuracy was significantly affected by stimulus type ($F[1, 119] = 6.784$, $p = 0.010$, partial $\eta^2 = 0.054$), with a higher number of correct responses observed in neutral ($M = 26.79$, $SEM = 0.217$) relative to emotional trials ($M = 25.79$, $SEM = 0.216$) regardless of time of assessment and type of treatment. As in the analysis of EI and RTs for neutral and emotional stimuli, we observed a significant interaction between treatment group, time and accuracy ($F[2, 119] = 5.679$, $p = 0.004$, partial $\eta^2 = 0.087$). Post-hoc tests revealed a significant increase ($p < 0.001$) in the number of correct answers to (aversive) emotional stimuli from pre- ($M = 25.01$, $SEM = 0.422$) to post-treatment ($M = 26.83$, $SEM = 0.382$) in the BMT group only (Figure 3).

Discussion

The present study investigated attentional and emotional control in patients with GAD using a cognitive task. We aimed to examine the effects of three different interventions on emotional interference in cognitive processing. Contrary to our hypothesis, BMT was no more effective than either QoL or FLX at decreasing the EI of aversive stimuli in patients with GAD. The medication was the only treatment to significantly reduce EI. The FLX and QoL groups did show a reduction in RT, suggesting an increased habituation rate to emotional stimuli. Additionally, as initially hypothesized, the BMT group showed a significant increase in the number of correct responses to emotional stimuli from pre- to post-treatment, suggesting improved attentional control.

To ensure the allocation of attentional resources to ongoing tasks proactive, top-down attention mechanisms are implemented, while reactive, bottom-up mechanisms are triggered by the appearance of new or salient information, such as emotional stimuli. These processes influence one another and are also strongly affected by emotion (43,44).

According to attention control theory, anxiety can reduce attention control functions and impair performance in executive functioning. In tasks with no threatening stimuli, individuals with anxiety disorders may be able to narrow their attention to relevant stimuli in the task at hand, displaying intact cognitive performance (45,46). In the present study, fluoxetine was the only treatment that effectively reduced the influence of aversive emotional stimuli on attentional and emotional processing. The influence of fluoxetine on attentional and emotional

tasks has been examined in a previous study where participants used the medication did not show emotion-potentiated startle responses, leading to improve cognitive performance. In light of these findings, the authors concluded that medication can modulate emotional processing (19). Another study evaluating fluoxetine and cognition in individuals with depression found that cognitive functioning improved after prolonged treatment with the drug (45) corroborating the results of the present study. Marwari & Dawe (2018) (20), suggested that the antidepressant effects of fluoxetine may help mitigate neurocognitive deficits, especially in spatial learning, memory and attention. The present findings also support the hypothesis that pharmacological treatment can change affective cognitive bias and reduce negative bias in accordance to previous studies.

Our initial hypothesis regarding the effects of different interventions on attentional and emotional control was that MBT, which focuses on mindfulness and awareness of emotions and sensations, would lead to a decrease in emotional interference. Previous studies have found that mindfulness-based interventions are associated with improvement in executive functions, including the inhibition of cognitive responses and reduced emotional interference by distractor stimuli (47,48). However, in the present study, we did not find any changes in emotional interference in the MBT group. These participants did, however, show a significant increase in the number of correct answers given in response to aversive emotional stimuli. This result corroborates with previous findings regarding the role of mindfulness in the monitoring and control of attentional performance, as a top-down process with a higher level of cognitive control (30,48–50) and in line with those on the effects of mindfulness training on emotion regulation in anxiety (26,51,52). Zhao et al (2019) (26), found that mindfulness-based cognitive therapy (MBCT) reduced anxiety and increased mindfulness and awareness in patients with mild to moderate GAD.

Information processing and attention control rely on separate but complementary neural pathways that include prefrontal regions associated with attentional processing, and the thalamic-amygdala pathway, which plays a role in threat detection (53). In the present study, trials involving emotional stimuli were associated with longer RTs across all treatment groups. These findings agree with those of previous studies showing that emotional stimuli capture attention more effectively than neutral stimuli (8). Faster responses to emotional information have been observed in tasks with aversive conditions (54) and angry or fearful facial expressions (55). RTs to emotional stimuli decreased over time in both the medication and QoL groups. This is indicative of improved bottom-up attentional processing of emotional information, which leads to faster habituation to aversive stimuli and, consequently, a shorter

RT. These results, combined with those of other studies (56) suggest that task performance might be affected by the appraisal of peripheral stimuli, which in this case, consisted of aversive images.

This study had some limitations. The interventions were administered over the course of 8 weeks, placing significant demands on the availability of participants and contributing to sample loss over time. Lastly, the cognitive task administered in the present study, though widely used, measures only attentional processing and EI; the use of a more comprehensive neuropsychological battery in addition to this task could add to the present findings by providing insight into the executive functions of these patients.

Despite these limitations, this was the first randomized clinical trial to compare the effects of three interventions on emotional and attentional processing in patients with GAD. Cognitive functioning in GAD has only been scarcely investigated, and the present study showed that the effects of these interventions on anxiety might be influenced by attentional and emotional processing, which could affect performance in attentional tasks. These findings showed that all three interventions could affect information processing and reactivity to dangerous or threatening stimuli. Our findings suggest that inhibition and cognitive control may be promising targets for new treatment strategies for GAD.

REFERÊNCIAS

1. American Psychiatric Association. Dsm-5: Manual Diagnóstico E Estatístico De Transtornos Mentais.5. ed. Porto Alegre: Artmed; 2014. 992 p.

2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas Kr, Walters Ee. Lifetime Prevalence And Age-Of-Onset Distributions Of Dsm-Iv Disorders In The National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593–602.

3. Cuthbert B, Insel T. The Data Of Diagnosis: New Approaches To Psychiatric Classification. Psychiatry: Interpersonal And Biological Processes. 2010 Dec;73(4):311–4.

4. Mennin DS, Fresco DM. What, Me Worry And Ruminate About *Dsm-5* And Rdoc? The Importance Of Targeting Negative Self-Referential Processing. Clin Psychol Sci Pract. 2013 Dec;20(3):258–67.

5. Botvinick Mm, Braver Ts, Barch Dm, Carter Cs, Cohen Jd. Conflict Monitoring And Cognitive Control. Psychological Review. 2001;108(3):624–52.

6. Gross JJ. Emotion Regulation: Taking Stock And Moving Forward. Emotion. 2013 Jun;13(3):359–65.

7. Newman MG, Llera SJ. A Novel Theory Of Experiential Avoidance In Generalized Anxiety Disorder: A Review And Synthesis Of Research Supporting A Contrast Avoidance Model Of Worry. Clin Psychol Rev. 2011 Apr;31(3):371–82.

8. Hallion LS, Tolin DF, Assaf M, Goethe J, Diefenbach GJ. Cognitive Control In Generalized Anxiety Disorder: Relation Of Inhibition Impairments To Worry And Anxiety Severity. Cogn Ther Res. 2017 Aug;41(4):610–8.

9. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The Unity And Diversity Of Executive Functions And Their Contributions To Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. Cognitive Psychology. 2000 Aug;41(1):49–100.

10. Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, Van Ijzendoorn MH. Threat-Related Attentional Bias In Anxious And Nonanxious Individuals: A Meta-Analytic Study. Psychological Bulletin. 2007;133(1):1–24.

11. Berggren N, Richards A, Taylor J, Derakshan N. Affective Attention Under Cognitive Load: Reduced Emotional Biases But Emergent Anxiety-Related Costs To Inhibitory Control. Front Hum Neurosci. 2013;7:188.

12. Derakshan N, Eysenck MW. Anxiety, Processing Efficiency, And Cognitive Performance: New Developments From Attentional Control Theory. European Psychologist. 2009 Jan;14(2):168–76.

13. Najmi S, Amir N, Frosio KE, Ayers C. The Effects Of Cognitive Load On Attention Control In Subclinical Anxiety And Generalised Anxiety Disorder. Cognition And Emotion. 2015 Oct 3;29(7):1210–23.

14. Beaudreau SA, O'hara R. The Association Of Anxiety And Depressive Symptoms With Cognitive Performance In Community-Dwelling Older Adults. Psychol Aging. 2009 Jun;24(2):507–12.

15. Price RB, Siegle G, Mohlman J. Emotional Stroop Performance In Older Adults: Effects Of Habitual Worry. The American Journal Of Geriatric Psychiatry. 2012 Sep;20(9):798–805.

16. Zainal NH, Newman MG. Worry Amplifies Theory-Of-Mind Reasoning For Negatively Valenced Social Stimuli In Generalized Anxiety Disorder. J Affect Disord. 2018 Feb;227:824–33.

17. Sanchez A, Everaert J, Koster Ehw. Attention Training Through Gaze-Contingent Feedback: Effects On Reappraisal And Negative Emotions. Emotion. 2016 Oct;16(7):1074–85.

18. Lenze EJ, Dixon D, Mantella RC, Dore PM, Andreescu C, Reynolds CF, et al. Treatment-Related Alteration Of Cortisol Predicts Change In Neuropsychological Function During Acute Treatment Of Late-Life Anxiety Disorder: Cortisol In Late-Life Anxiety And Improved Memory. Int J Geriatr Psychiatry. 2012 May;27(5):454–62.

19. Capitão LP, Murphy SE, Browning M, Cowen PJ, Harmer CJ. Acute Fluoxetine Modulates Emotional Processing In Young Adult Volunteers. Psychol Med. 2015 Aug;45(11):2295–308.

20. Marwari S, Dawe GS. (R)-Fluoxetine Enhances Cognitive Flexibility And Hippocampal Cell Proliferation In Mice. J Psychopharmacol. 2018 Apr;32(4):441–57.

21. Klumpp H, Fitzgerald Da, Angstadt M, Post D, Phan Kl. Neural Response During Attentional Control And Emotion Processing Predicts Improvement After Cognitive Behavioral Therapy In Generalized Social Anxiety Disorder. Psychol Med. 2014 Oct;44(14):3109–21.

22. Pishyar R, Harris LM, Menzies RG. Responsiveness Of Measures Of Attentional Bias To Clinical Change In Social Phobia. Cognition & Emotion. 2008 Nov;22(7):1209–27.

23. Hoge EA, Bui E, Marques L, Metcalf CA, Morris LK, Robinaugh DJ, et al. Randomized Controlled Trial Of Mindfulness Meditation For Generalized Anxiety Disorder: Effects On Anxiety And Stress Reactivity. J Clin Psychiatry. 2013 Aug 15;74(08):786–92.

24. Roemer L, Orsillo SM. An Open Trial Of An Acceptance-Based Behavior Therapy For Generalized Anxiety Disorder. Behavior Therapy. 2007 Mar;38(1):72–85.

25. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development And Validation Of A Structured Diagnostic Psychiatric Interview For Dsm-Iv And Icd-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;Quiz 34-57.

26. Zhao X, Chen Z, Kang C, Liu R, Bai J, Cao Y, et al. Mindfulness-Based Cognitive Therapy Is Associated With Distinct Resting-State Neural Patterns In Patients With Generalized Anxiety Disorder. Asia-Pacific Psychiatry [Internet]. 2019 Dec [cited 2020 Oct 26];11(4). Available from: Https://Onlinelibrary.Wiley.Com/Doi/Abs/10.1111/Appy.12368

27. Costa MA, Gonçalves FG, Tatton-Ramos T, Fonseca NKOD, Schwinn JK, Alves SG, et al. A Three-Arm Randomized Clinical Trial Comparing The Efficacy Of A Mindfulness-Based Intervention With An Active Comparison Group And Fluoxetine Treatment For Adults With Generalized Anxiety Disorder. Psychother Psychosom. 2020 Dec 15:1-11.

28. Russell T. Body In Mind Training: Mindful Movement For Severe And Enduring Mental Illness. British Journal Of Wellbeing. 2011 Apr;2(4):13–6.

29. Erthal FS, De Oliveira L, Mocaiber I, Pereira Mg, Machado-Pinheiro W, Volchan E, et al. Load-Dependent Modulation Of Affective Picture Processing. Cogn Affect Behav Neurosci. 2005 Dec;5(4):388–95.

30. Menezes CB, De Paula Couto MC, Buratto LG, Erthal F, Pereira MG, Bizarro L. The Improvement Of Emotion And Attention Regulation After A 6-Week Training Of Focused Meditation: A Randomized Controlled Trial. Evid Based Complement Alternat Med. 2013;2013:1–11.

31. Lang PJ, Bradley MM, Cuthbert. International Affective Picture System (Iaps): Affective Ratings Of Pictures And Instruction Manual. Technical Report A-6. Gainesville, Fl: University Of Florida; 2005.

32. Hamilton M. The Assessment Of Anxiety States By Rating. Br J Med Psychol. 1959;32(1):50–5.

33. Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, et al. Reliability And Validity Of A Structured Interview Guide For The Hamilton Anxiety Rating Scale (Sigh-A). Depress Anxiety. 2001;13(4):166–78.

34. Desousa DA, Moreno AL, Gauer G, Manfro GG, Koller SH. Revisão Sistemática De Instrumentos Para Avaliação De Ansiedade Na População Brasileira. Avali Psicol. 2013;12(3):13.

35. Galluci Neto J GN J, Campus Junior MS, Hubner CK. Escala De Depressão De Hamilton (Ham-D): Revisão Dos 40 Anos De Sua Utilização. 2001;3(1):6.

36. Hamilton M. Development Of A Rating Scale For Primary Depressive Illness. British Journal Of Social And Clinical Psychology. 1967 Dec;6(4):278–96.

37. Carneiro AM, Fernandes F, Moreno RA. Hamilton Depression Rating Scale And Montgomery–Asberg Depression Rating Scale In Depressed And Bipolar I Patients: Psychometric Properties In A Brazilian Sample. Health Qual Life Outcomes. 2015 Dec;13(1):42.

38. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Aplicação Da Versão Em Português Do Instrumento Abreviado De Avaliação Da Qualidade De Vida "Whoqol-Bref". Rev Saúde Pública. 2000 Apr;34(2):178–83.

39. Cancian ACM, Souza Las De, Silva VHP E, Machado W De L, Oliveira M Da S. Psychometric Properties Of The Brazilian Version Of The Difficulties In Emotion Regulation Scale (Ders). Trends Psychiatry Psychother. 2019 Mar;41(1):18–26.

40. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development And Validation Of The Penn State Worry Questionnaire. Behaviour Research And Therapy. 1990;28(6):487–95.

41. Beck AT. Cognitive Therapy And Emotion Disorders. New York: International Universities Press; 1976.

42. Castillo C, Macrini L, Cheniaux E, Landeira-Fernandez J. Psychometric Properties And Latent Structure Of The Portuguese Version Of The Penn State Worry Questionnaire. Span J Psychol. 2010 May;13(1):431–43.

43. Kim H, Somerville Lh, Johnstone T, Polis S, Alexander Al, Shin Lm, Et Al. Contextual Modulation Of Amygdala Responsivity To Surprised Faces. J Cogn Neurosci. 2004 Dec;16(10):1730–45.

44. Pessoa L, Japee S, Sturman D, Ungerleider LG. Target Visibility And Visual Awareness Modulate Amygdala Responses To Fearful Faces. Cerebral Cortex. 2006 Mar 1;16(3):366–75.

45. Cassano GB, Puca F, Scapicchio PL, Trabucchi M, Italian Study Group On Depression In Elderly Patients. Paroxetine And Fluoxetine Effects On Mood And Cognitive Functions In Depressed Nondemented Elderly Patients. J Clin Psychiatry. 2002 May;63(5):396–402.

46. Gonda X, Pompili M, Serafini G, Carvalho AF, Rihmer Z, Dome P. The Role Of Cognitive Dysfunction In The Symptoms And Remission From Depression. Ann Gen Psychiatry. 2015 Dec;14(1):27.

47. Baker AW, Frumkin MR, Hoeppner SS, Leblanc NJ, Bui E, Hofmann SG, et al. Facets Of Mindfulness In Adults With Generalized Anxiety Disorder And Impact Of Co-Occurring Depression. Mindfulness. 2019 May;10(5):903–12.

48. Teper R, Inzlicht M. Meditation, Mindfulness And Executive Control: The Importance Of Emotional Acceptance And Brain-Based Performance Monitoring. Social Cognitive And Affective Neuroscience. 2013 Jan 1;8(1):85–92.

49. Kozasa EH, Sato JR, Lacerda SS, Barreiros MAM, Radvany J, Russell TA, et al. Meditation Training Increases Brain Efficiency In An Attention Task. Neuroimage. 2012 Jan;59(1):745–9.

50. Slagter HA, Lutz A, Greischar LL, Francis AD, Nieuwenhuis S, Davis JM, et al. Mental Training Affects Distribution Of Limited Brain Resources. Rugg Md, Organizador. Plos Biol. 2007 May 8;5(6):E138.

51. Zeidan F, Martucci KT, Kraft RA, Mchaffie JG, Coghill RC. Neural Correlates Of Mindfulness Meditation-Related Anxiety Relief. Soc Cogn Affect Neurosci. 2014 Jun;9(6):751–9.

52. Zhang Q, Wang Z, Wang X, Liu L, Zhang J, Zhou R. The Effects Of Different Stages Of Mindfulness Meditation Training On Emotion Regulation. Front Hum Neurosci. 2019 Jun 27;13:208.

53. Bishop SJ. Neural Mechanisms Underlying Selective Attention To Threat. Ann N Y Acad Sci. 2008 May;1129(1):141–52.

54. Astudillo C, Muñoz K, Maldonado PE. Emotional Content Modulates Attentional Visual Orientation During Free Viewing Of Natural Images. Front Hum Neurosci. 2018 Nov 15;12:459.

55. Lobue V. More Than Just Another Face In The Crowd: Superior Detection Of Threatening Facial Expressions In Children And Adults. Developmental Science. 2009 Mar;12(2):305–13.

56. Oldrati V, Bardoni A, Poggi G, Urgesi C. Influence Of Attention Control On Implicit And Explicit Emotion Processing Of Face And Body: Evidence From Flanker And Same-Or-Different Paradigms. Front Psychol. 2020 Jan 21;10:2971.

Table 1 - Clinical characteristics of the three treatment groups at baseline.

	FLX		BMT		QoL				
	Mean	SEM	Mean	SEM	Mean	SEM	*F*	*p*	*partial η²*
Age	36.69	1.52	33.14	1.57	35.53	1.51	1.356	0.260	0.013
HAM-A	27.690	1.11	28.276	1.11	28.000	1.16	0.070	0.933	0.001
HAM-D	13.603	0.64	14.483	0.64	15.283	0.67	1.631	0.199	0.019
WHOQOL-Bref	76.569	1.29	74.483	1.29	76.453	1.35	0.811	0.446	0.010
PSWQ	49.379	1.05	51.345	1.05	49.094	1.10	1.327	0.268	0.016
DERS	114.517	2.22	113.966	2.22	113.491	2.32	0.051	0.950	0.001

Notes: FLX: Fluoxetine group; BMT: Mindfulness group; QoL: Active control; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; WHOQOL-Bref: World Health Organization Quality of Life questionnaire; PSWQ: Penn State Worry Questionnaire; DERS: Difficulties in Emotion Regulation Scale.

Table 2 - Reaction times for each stimulus type on pre- and post-treatment assessments.

		Pre-Treatment		Post-Treatment		
		Mean	SEM	Mean	SEM	p^a
FLX	RT-Emotional	775.62	25.75	670.37	20.39	0.001**
	RT-Neutral	736.65	24.13	659.02	18.63	0.002*
BMT	RT-Emotional	702.05	22.70	676.64	17.98	0.285
	RT-Neutral	682.62	21.28	658.25	16.43	0.305
QoL	RT-Emotional	751.96	27.07	670.42	21.44	0.003*
	RT-Neutral	730.26	25.37	654.93	19.59	0.005*

Note: * p < 0.05; ** p < 0.001; FLX: Fluoxetine group; BMT: Mindfulness group; QoL: Active control; RT: Reaction Time; SEM: Standard Error of the Mean; [a] Values obtained from Bonferroni post hoc tests.

Figure 1 - Cognitive Discrimination Task

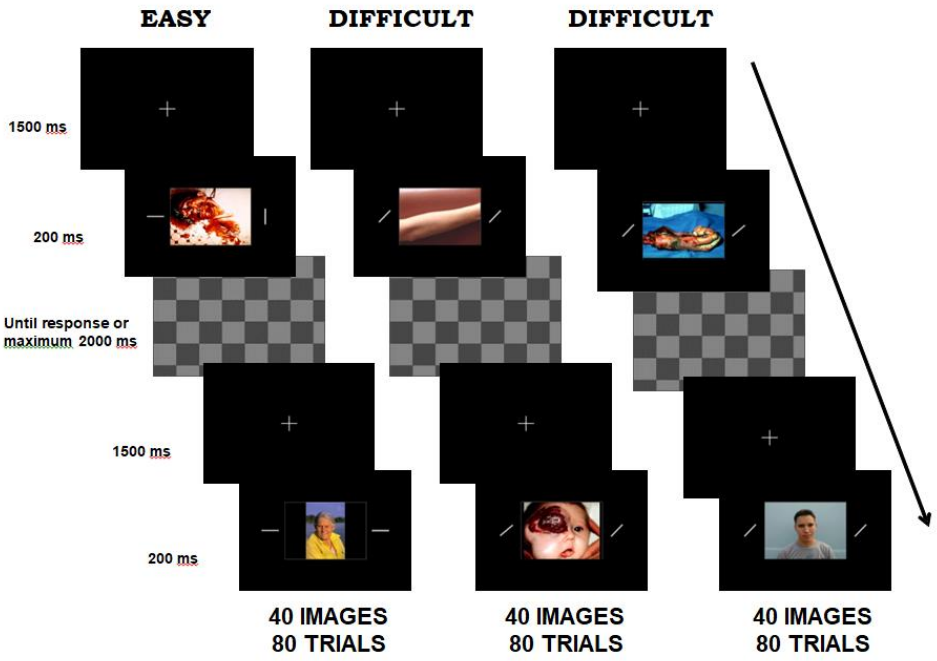
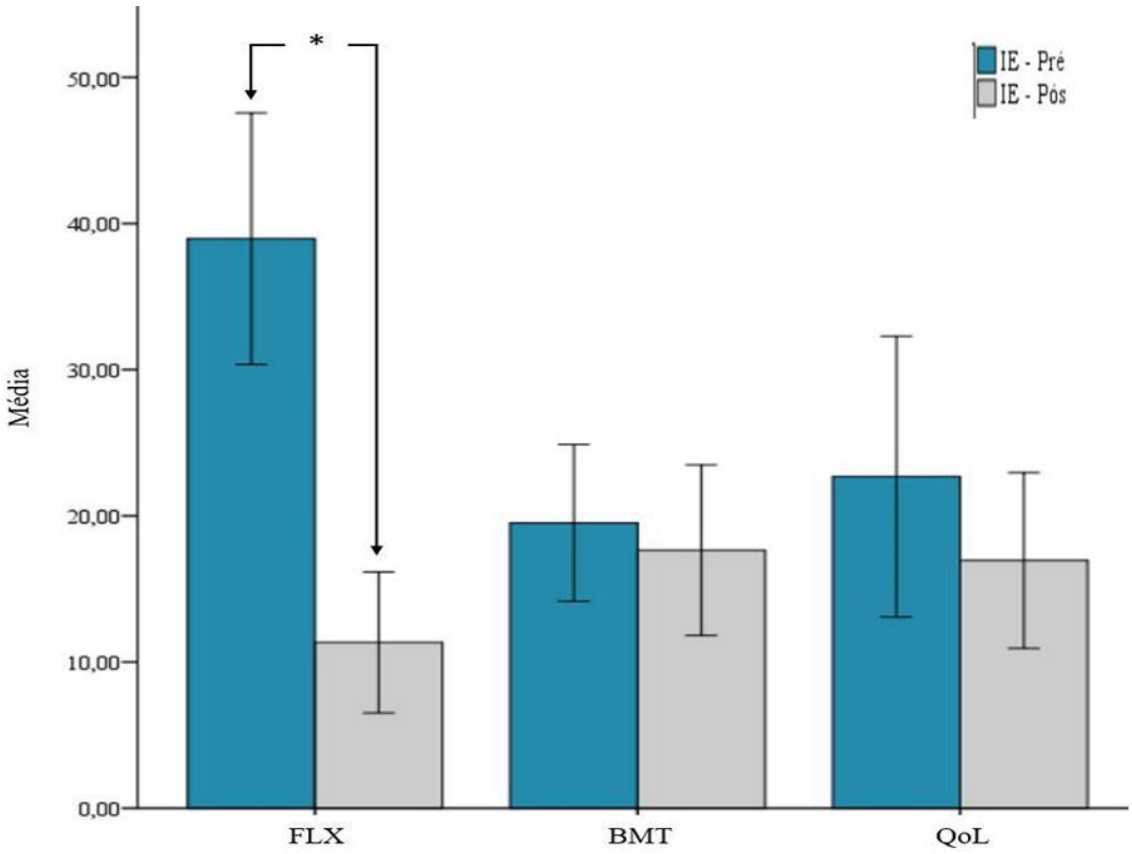


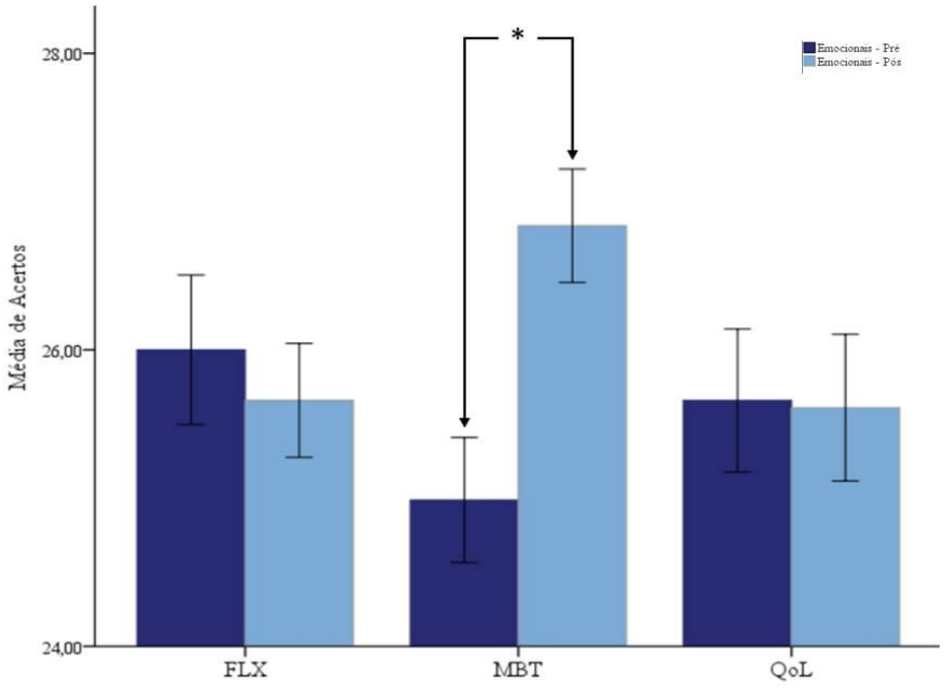
Figure 2 - Effects of treatment on emotional interference (EI) scores throughout the task.



Note: *Values* represent the mean score for each trial block (D1, D2 and E). *, $p = 0.001$.

Figure 3 - Mean and standard error of correct responses to emotional stimuli before and after the intervention.

Note: A significant increase in correct responses was observed in the MBT group.



* $p < 0.001$.

14.3 Artigo 3

A group quality-of-life protocol as a clinical intervention for the treatment of patients with generalized anxiety disorder

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Key words: generalized anxiety disorder, anxiety, quality of life, wellbeing, group therapy

Abstract

Introduction: Generalized anxiety disorder (GAD) has a major negative impact on several domains of quality of life (QoL). **Objective:** To present a protocol for changing habits to promote quality of life for patients with GAD and compare a series of clinical measures before and after the intervention. **Methods:** Subgroup analysis of a three-arm randomized clinical trial which compared the efficacy of psychoactive drugs versus a mindfulness-based intervention and the QoL and psychoeducation intervention in patients with GAD. **Results:** In the original trial, 84 subjects were allocated to receive the QoL and psychoeducation intervention. When comparing parameters over time in this treatment arm, all Hamilton Anxiety Rating Scale (HAM-A) scores significantly reduced from baseline to week 5 and week 8, with no significant difference between these last 2 weeks. WHOQOL physical, psychological, and global domain scores also increased significantly from baseline to week 5 and week 8. **Conclusions:** A QoL and psychoeducation protocol proved effective in reducing anxiety and improving QoL in subjects with GAD. As the protocol is suitable for application by non-specialist health professionals, these findings should contribute to improving management of GAD.

INTRODUCTION

Generalized anxiety disorder (GAD) is characterized by persistent and excessive anxiety and worry that are difficult to control and last at least 6 months. Associated symptoms include irritability, fatigue, sleep problems, difficulty concentrating, and somatic symptoms such as muscle tension (1). Patients with GAD usually worry about occupational, social, and everyday problems. This is associated with reduced quality of life caused by physical and emotional problems (1–3). In the general population, the 12-month prevalence of GAD is 3.1%, while the lifetime prevalence is approximately 6% (4).

It is one of the most common mental disorders in primary care, and is associated with increased utilization of health resources and disability (5). Anxiety is closely linked to population-wide morbidity: it is the second leading cause of absenteeism from work and a potential driver of the development of more severe disorders (1,4,5). Despite imposing significant emotional and physical suffering, with loss of quality of life (QoL) and occupational impairments, GAD is still underdiagnosed and undertreated (3,6). Considering this gap and the high prevalence and consequences of GAP for the individual, it is important that easily applied interventions be accessible to non-specialist health professionals rather than psychologists or psychiatrists alone.

Group interventions, whose main function is to provide health education and improve individual ability to achieve good QoL, are one such possibility. The group intervention process not only allows individuals to learn about their disorder, but also provides a venue for socializing, integrating, and exchanging lived experiences. Group models can offer opportunities for more positive peer modeling, reinforcement, and social support (7) The use of group interventions to promote quality of life is one of several fertile fields to foster individual autonomy and improve function(8). Individuals with anxiety can benefit from these interventions through psychoeducation, where theoretical and practical information is imparted in order to promote, prevent, and educate individuals about health and well-being and enable them to apply these tools in their daily lives. When individuals achieve a good understanding of their anxiety, they learn new skills to better deal with their emotions and become their own therapists (9).

Furthermore, it is well established that many nonspecific therapeutic factors observed in therapies are observed in group interventions as well, such as the effects of the facilitator’s attention, group engagement, participant characteristics, the therapeutic alliance, and processes involved in therapeutic change (10). Among several potential mechanisms of change, the

therapeutic alliance is particularly foundational. Studies have shown that the key characteristics of the therapist or "facilitator" which contribute to the development of a therapeutic alliance are empathy, openness, cordiality, trust, and the use of self-disclosure (11,12).

Within this context, the objective of the present study is twofold: 1) to describe a QoL and psychoeducation intervention protocol used in a three-arm randomized clinical trial which compared the efficacy of a psychoactive drug versus a mindfulness-based intervention and the aforementioned intervention in patients with GAD (13); and 2) to conduct a subgroup analysis of efficacy of this QoL and psychoeducation intervention protocol in individuals allocated to receive it, considering anxiety symptoms and QoL scores before, during, and after the end of the intervention.

METHODS

Participants

The sample consisted of 84 subjects with GAD who were recruited through media advertisements at Hospital de Clinicas de Porto Alegre (HCPA) for a randomized clinical trial for the treatment of GAD. Regarding the inclusion criteria, we selected those individuals who were aged >18 years, had GAD as their primary diagnosis by the Mini-International Neuropsychiatric Interview (MINI), and were able to attend weekly sessions at the hospital for 8 weeks. Individuals who were under psychopharmacological or psychotherapeutic treatment for GAD, who had a previously failed a trial of fluoxetine treatment for GAD or were intolerant of fluoxetine, had a diagnosis of bipolar disorder, psychotic disorder, substance use disorder (except tobacco) in the last 6 months, or suicidal ideation in the last 6 months (assessed using the MINI), a Hamilton Anxiety Rating Scale (HAM-D) score ≥23 at baseline assessment, contraindications to SSRI use (use of thioridazine or monoamine oxidase inhibitors [IMAO], coagulopathy, current anticoagulant use, current antiretroviral therapy), contraindications to mindfulness-based interventions (clinical instability or immobility), were pregnant or breastfeeding, or had antisocial personality disorder (also assessed using the MINI) were excluded.

Research instruments

Sociodemographic measures

Sociodemographic level was assessed by means of the 2015 Brazilian economic classification criterion.

Mini-International Neuropsychiatric Interview (MINI)

The MINI consists of a structured, validated diagnostic interview that allows the investigator to make psychiatric diagnoses based on DSM-IV and ICD-10 criteria (14). It has been validated for the Brazilian population. For the present study, adaptations were made to take into account the changes from DSM-IV to DSM-5.

Generalized Anxiety Disorder 7-item scale (GAD-7)

The GAD-7 is a brief, validated, self-report scale with proven efficacy in screening for and measuring the severity of GAD (15).

Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a widely used and well-validated scale developed to quantify the severity of anxiety symptoms (16). Scores between 14 and 17 are indicative of mild anxiety. Scores of 18 to 24 indicate mild to moderate anxiety. Finally, scores of 25 to 30 denote moderate to severe anxiety.

WHOQOL-Bref

The WHOQOL-Bref is a 26-item scale that measures quality of life, consisting of 2 general questions and 24 that represent each of the domains that make up the instrument. These are physical, psychological, social relationships, and environment. It has been validated for use in Brazil (17).

Penn State Worry Questionnaire (PSWQ)

The PSWQ is a self-report scale developed to measure the trait of worry. (18,19)It consists of 16 Likert-type items, scored from 1 to 5, which assess the generality, excessiveness, and uncontrollability of worry, and has good ability to discriminate individuals with GAD. A psychometric evaluation of the Portuguese version showed adequate internal consistency(20).

Clinical Global Impression (CGI)

The CGI determines the overall severity of a mental disorder. Scores range from 1 (normal, not at all ill) to 7 (extremely ill) (21).

Procedures

Assessment

Initial screening was carried out by telephone application of the GAD-7. Potential participants who were receiving psychological or psychiatric treatment, had previous unsuccessful trials of fluoxetine therapy, or were pregnant or breastfeeding were excluded. Based on these established criteria, the selected subjects were personally interviewed by trained psychologists and psychiatrists who administered the MINI, HAM-A, HAM-D, and CGI and double-checked the exclusion criteria. The other self-report questionnaires were completed on weeks 0, 5, and 8. Blinded analysis took place at weeks 5 and 8, with administration of the HAM-A and CGI by trained psychologists and psychiatrists. All subjects were assessed before and after the 8-week intervention.

Intervention: Quality-of-life group

The QoL group consisted of 8 weeks of 2-hour weekly sessions, conducted by a psychologist with experience in group interventions, held at a dedicated group intervention room at Hospital de Clinicas de Porto Alegre (HCPA). QoL themes with proven impact in terms of reducing anxiety symptoms were chosen for the sessions(22). During each meeting, a topic was presented in the form of a class: the facilitator showed a slide deck, which was followed by a group discussion of the presented topic. Participants were encouraged to share personal issues related to anxiety and how they perceived it in their daily lives, as well as discuss the

influence of their daily habits on anxiety. At the end of each session, each participant was assigned homework related to the topic addressed on the day. A WhatsApp group was created to exchange relevant information about anxiety and related themes and share homework assignments. The participants frequently posted messages celebrating their success in carrying out the assigned tasks, which motivated and reinforced the behavior of other group members. A detailed description of the group meetings is given below.

Session 1: *Psychoeducation on GAD*

During the first session, participants received psychoeducation on anxiety and GAD. Participants were taught to identify the cognitive (constant worrying, attention and concentration issues, memory issues, minor "blackouts"), emotional (irritability, sadness), physiological (tachycardia, sweating, shortness of breath, agitation, muscle tension), and behavioral (avoidance, procrastination, hypervigilance) symptoms of anxiety. All were given the opportunity to discuss the presentation, share their main symptoms, and discuss how they perceived anxiety in their lives. The diaphragmatic breathing technique was introduced as a first-line resource for anxiety management (23). At the end of the session, participants were assigned homework—namely, to practice diaphragmatic breathing throughout the week.

Session 2: *Substance use*

During the second session, participants were given psychoeducation about the relationship between anxiety and substance use. Substance abuse may be associated with the need for relief from anxiety and negative emotions in the short term; however, in the medium and long term, anxiety remains and can even intensify with continued use, with emotional, physical, and functional consequences. Participants were introduced to the process of changing habits through the motivational stages of change: pre-contemplation, contemplation, preparation, action, and maintenance (24). At the end of the session, participants were assigned homework—namely, to review their substance use and plan changes of habit.

Session 3: *Sleep hygiene*

During the third session, participants were given psychoeducation about the relationship between anxiety and sleep. The facilitator explained that many insomniacs develop negative sleep conditioning and start to panic as bedtime approaches. Relaxing activities close to bedtime and management of worries and ruminative thoughts were suggested as ways to address this. Participants were introduced to sleep hygiene techniques so they could practice small changes

in habits for more restful sleep (25). At the end of the session, participants were assigned homework—namely, to practice sleep hygiene throughout the week.

- Internal clock:
- Get just enough sleep to feel refreshed.
- Take 10-to-15-minute naps as needed.
- Keep a regular sleep schedule.
- If you wake up in the middle of the night, avoid exposure to strong lights.
- Expose yourself to sunlight immediately after waking up in the morning.
- Avoid using your phone, watching television, or handling other electronic devices around bedtime.
- Refrain from consuming caffeinated beverages.

Session 4: *Physical activity*

During the fourth session, participants were given psychoeducation about the relationship between anxiety and physical activity. The facilitator presented scholarly articles proving that aerobic physical exercise reduces anxiety, with results similar to those achieved through meditation and relaxation strategies, because exercise triggers the release of neurotransmitters associated with well-being and pleasure (26). The facilitator further noted that all those who suffer from anxiety need to adopt regular physical exercise as a tool to reduce its symptoms. At the end of the session, participants were assigned homework—namely, to find a way to exercise.

Session 5: *Healthy eating*

During the fifth session, participants were given psychoeducation about the relationship between anxiety and eating. Key foods and beverages that contribute to increased anxiety and impact on QoL were presented. Alongside this, participants were encouraged to work on eating behavior, recognition of our relationship with food, and how we use diet as a strategy to alleviate our anxiety through eating, especially sugars and other carbohydrates (27). At the end of the session, participants were assigned homework—namely, to choose a change to make in their eating habits.

Session 6: *Review of points discussed and maintenance process.*

Session 7: *Review of points discussed and maintenance process.*
Session 8: *Group closure and review of gains achieved over the course of the intervention.*

STATISTICAL ANALYSIS

Quantitative variables with normal distribution were expressed as mean and standard deviation, and categorical variables, as absolute and relative frequencies. Student's *t*-test for independent samples was used to compare means between normally distributed variables. Pearson's chi-square test or Fisher's exact test were used to compare proportions.

To compare parameters over time, a generalized estimating equations (GEE) model with Bonferroni correction was used. The significance level was set at 5% ($p \leq 0.05$), and all analyses were carried out in SPSS 21.0.

RESULTS

Baseline

Participants were included from January 2017 to August 2018. The first group of participants started treatment in March 2017, and the last ended treatment in December 2018. A total of 84 subjects who participated in the QoL group were selected; of these, 38 completed the study. The sample consisted mainly of female patients (81%, n=68), and the mean (SD) age was 34.0 (11.2) years. Most participants had a high level of education (completed secondary school or higher).

Attrition

When comparing subjects who dropped out of the study to those who completed it, those who dropped out were significantly younger than those who did not drop out (mean age, 27.9 ± 7.6 vs 36.7 ± 11.5 years, respectively; $p < 0.001$). The total HAM-A score at baseline was also significantly lower in those who dropped out of the intervention (24.3 ± 7.2 vs 29.4 ± 7.3; $p=0.014$). The other characteristics did not differ significantly between groups ($p>0.05$).

Table 1 – Sample profile

Variable	n=84
Age (years), mean ± SD	34.0 ± 11.2
Sex, n (%)	
Female	68 (81.0)
Male	16 (19.0)
Educational attainment, n (%)	
Completed High School	20 (24.4)
Incomplete High School	2 (2.4)
Full Higher Education	16 (19.5)
Incomplete Higher Education	31 (37.8)
Postgraduate/Graduate courses	13 (15.9)
Economic class, n (%)	
B	39 (48.8)
C	39 (48.8)
Post	2 (2.5)
Psychotherapy, n (%)	3 (3.6)
Mental disorders, n (%)	
Major depression	35 (41.7)
Panic disorder	14 (16.7)
Agoraphobia	17 (20.2)
Social anxiety disorder	14 (16.7)
Obsessive-compulsive disorder	5 (6.0)

When comparing clinical parameters over time, HAM-A scores significantly reduced from baseline to week 5 and week 8, with no significant difference between these last 2 weeks. The mean initial total score declined from (SD=28.2) to (SD=20.7) at week 8 (Table 2).

As shown in Table 2, CGI scores also reduced significantly from pre-intervention levels (mean, 4.5) to week 5 (mean, 3.8) and week 8 (mean, 3.4), with no significant difference between these last 2 weeks.

WHOQOL physical, psychological, and global domain scores also increased significantly from baseline to week 5 and week 8, with no significant difference between these last 2 weeks. For the social domain, the increase in week 8 was is significant compared to the others. PSWQ scores reduced significantly over time, at all three time points respectively (Table 2).

After a follow-up period of 2 years after the end of the intervention, the behavior of these subjects and their maintenance of the QoL habits developed during the intervention were evaluated. Of the 32 subjects analyzed over the 2-year longitudinal period, 24 (75%) were still practicing some of the topics covered in the QoL group and 8 (25%) did not practice any topic. Of these 24 subjects who practiced the exercises, 3 (15.5%) practiced them always, 8 (33.3%) practiced them often, 4 (16.6%) practiced them sometimes, and 5 (20.8%) practiced them

occasionally. Four participants (16.6%) did not report their practice frequency. The practiced topics included physical exercise, healthy eating, sleep hygiene, management of substance use, and use of a support network.

Table 2 – Comparison of parameters over time

Variable	n	Baseline	n	5 weeks	N	8 weeks	p
		Mean ± SD		Mean ± SD		Mean ± SD	
HAM-A-S	69	12.5 ± 5.3[b]	35	8.1 ± 5.2[a]	38	8.6 ± 5.9[a]	<0.001
HAM-A-P	69	15.7 ± 3.4[b]	35	11.4 ± 5.8[a]	38	12.1 ± 6.3[a]	<0.001
HAM-A Total	69	28.2 ± 7.6[b]	35	19.5 ± 9.8[a]	38	20.7 ± 11.6[a]	<0.001
CGI.s	66	4.5 ± 0.7[b]	35	3.8 ± 1.3[a]	38	3.4 ± 1.4[a]	<0.001
WHOQOL-Bref							
Phys	60	49.0 ± 15.5[a]	35	53.7 ± 15.4[b]	35	59.9 ± 18.0[b]	<0.001
Psych	60	43.0 ± 14.7[a]	35	52.7 ± 16.3[b]	35	53.9 ± 17.5[b]	<0.001
Social	60	50.7 ± 17.8[a]	35	53.3 ± 18.4[a]	35	58.8 ± 16.2[b]	<0.001
Enviro	60	49.7 ± 12.5	35	52.8 ± 14.4	35	53.0 ± 15.1	0.093
Global	60	43.8 ± 18.8[a]	35	57.1 ± 17.2[b]	35	54.4 ± 17.9[b]	<0.001
PSWQ	59	60.6 ± 8.4[c]	35	54.8 ± 10.3[b]	35	44.0 ± 8.7[a]	<0.001

[a,b,c] Same superscript letter denotes no significant difference at the 5% level (Bonferroni's test).

DISCUSSION

In the present study, we tested the validity of a group psychoeducation and QoL intervention protocol for patients with GAD. All participants who completed the study (n=35) experienced significant reductions in anxiety and CGI scores, proving the effectiveness of the protocol for reducing anxiety symptoms through group psychoeducation on a series of factors related to anxiety and change-of-habit guidance.

Longitudinal comparison of the parameters of interest showed that, while the severity of anxiety symptoms, assessed using the HAM-A and CGI measures, decreased over time, QoL as assessed by the WHOQOL-Bref instrument increased significantly from baseline to week 5 and week 8, with no significant difference between these last two time points. This finding suggests that a 5-week intervention protocol might yield similar results compared to an 8-week intervention.

The behavioral outcomes observed after 2 years of follow-up indicated that 75% of group participants maintained their QoL habits. This rate is consistent with previous studies of group treatment for anxiety disorders, which also reported long-term reduction of anxiety symptoms and maintenance of gains obtained through the intervention. Research has proven the effectiveness of group cognitive-behavioral group therapy (CBGT) for anxiety disorders (28–30). CBGT has been shown to be an effective long-term intervention (4.6-year follow-up) for the treatment of social anxiety (28)and for panic disorder, with 50% symptom reduction at 3-month, 1-year, and long-term follow-up (31). A randomized clinical trial examining the efficacy of a 12-week diagnosis-agnostic group cognitive-behavioral intervention, compared to specific CBGT protocols for panic disorder, social anxiety disorder, and GAD, suggested significant improvement in anxiety in both groups and treatment equivalence in both approaches (32). Another study examined the long-term results of individual CBT and CBGT in 139 young adults with anxiety disorders. At reassessment 3.9 years after treatment, 63% of participants no longer met diagnostic criteria for major anxiety, and significant reductions were observed in all measures of anxiety symptoms (30).

In another study, 73 older adults with GAD who received CBGT were compared to a control group. The results showed improvement in symptoms both after the intervention and at 6-month follow-up (33). A case-control study of CBGT in 52 patients with GAD found that the intervention group experienced improvement in all variables, and that gains were maintained over 2 years of follow-up (22). A study of 11 subjects with GAD found that a mindfulness-based cognitive therapy (MBCT) protocol was potentially effective in improving anxiety and mood and increasing awareness of daily experiences(34). Another study evaluated 93 participants with GAD who were assigned to an 8-week Mindfulness-Based Stress Reduction (MBSR) group intervention or to an attention control. Both interventions yielded positive results, although the MBSR group had a significantly greater reduction in anxiety (35). One study found that short-term CBGT can downregulate abnormally higher connectivity of the prefrontal-amygdala network in patients with GAD, leading to clinical improvement (36).

The findings of our study is consistent with prior research on group interventions for anxiety disorders which showed reduction of anxiety symptoms, although our intervention is uniquely feasible, in that it can be facilitated and coordinated by providers without experience in CBT and can be delivered in primary-care settings.

Another aspect to be considered is the nonspecific factors that contribute to the effectiveness of psychotherapy. Previous studies have proven the efficacy of group therapy due to activation of psychological mechanisms that are not stimulated in individual

psychotherapeutic environments; these are known as nonspecific therapeutic factors (37,38). A previous review noted that nonspecific factors, such as the therapeutic relationship, have a major impact on patients' clinical improvement. Among the nonspecific factors, group cohesion is the most important factor in promoting the patient improvement as compared to any other specific technique used by the therapist (39). Studies have claimed that the main nonspecific factors associated with therapeutic improvement include expressed emotion, group cohesion, and the therapeutic alliance (40–42). Another study identified cohesion, universality, and self-analysis (self-understanding) as important aspects in the group therapeutic experience (43). Although we did not measure the group factors involved in the therapeutic process, we can infer that the group process significantly contributed to participants' improvement. This claim is supported by our observation of integration, cohesion, and exchange among the group members, which both occurred during the weekly meetings and was expressed verbally in the WhatsApp group.

There are some limitations in our study. The interventions lasted 8 weeks, which required the participants to be available for a rather long period. Thus, some attrition occurred. As this was a randomized clinical trial, participants could not choose their group and were randomly allocated, which may have contributed to the attrition rate at week 1 among participants who were not satisfied with the selected group and dropped out of treatment. Participants who dropped out of the study at week 1 were characterized by a younger age and lower total HAM-A scores, which may have contributed to a lower motivation for treatment. It is known that patients with shorter disease duration and milder symptoms experience less impairment and, possibly, greater functionality. As adherence to the assigned homework tasks was not measured, it cannot be associated with improvement in symptoms or lack thereof.

These limitations notwithstanding, this is an innovative analysis of a pioneering study (13) which assessed the application of a QoL protocol in patients with GAD. Utilization of mental health services is increasing, and with it a need for better care, higher levels of patient satisfaction, and improved health outcomes (44,45). In this sense, some institutions have included user engagement and participation in the accreditation of training programs for health professionals, seeking to better guide interventions and skills to be developed in response to the scarcity of mental health services and specialized professionals (45,46). These data are in line with our study on the applicability of a QoL protocol administered by trained non-mental health professionals. This could be a cost-effective treatment modality and particularly helpful in places where no dedicated mental health professionals are available.

In our study, we observed clear therapeutic effects of this intervention, decreasing anxiety, reducing levels of worry, and improving all measured QoL domains in the participants. Furthermore, changes in habits and practices seemed to be maintained over time by most participants, which highlights the need to continue QoL practices beyond the duration of treatment. In short, this study presents a novel, effective therapeutic intervention based on behavioral change and development of functional strategies to reduce anxiety.

CONCLUSIONS

The QoL intervention tested in this study allowed us to explore group tools and resources in the process of improving anxiety and associated symptoms. We found that small changes in lifestyle habits, such as proper sleep hygiene, eating, exercising, and time management, among others, contribute to healthier functioning and, consequently, a significant reduction in anxiety. This intervention is a feasible resource for all those who suffer from anxiety and can be implemented by a wide range of health professionals, who can be trained in the protocol without the need for any specialist training in psychotherapies. The methods can be used in institutional settings, primary health, hospitals, schools, corporate environments, and in private practice, and can be applied in groups or individually. The program is not only meant for individuals with a mental disorder; anyone can benefit from its techniques and tools to reduce anxiety by improving QoL. New group interventions can be trialed in various fields and institutional settings in order to provide communities with excellent mental, physical, and emotional health services.

REFERÊNCIAS

1. American Psychiatric Association. DSM-5: manual diagnóstico e estatístico de transtornos mentais. 5. ed. Porto Alegre: Artmed; 2014. 992 p.

2. Hu MX, Milaneschi Y, Lamers F, Nolte IM, Snieder H, Dolan CV, et al. The association of depression and anxiety with cardiac autonomic activity: The role of confounding effects of antidepressants. Depress Anxiety. 2019 Dec;36(12):1163–72.

3. Revicki DA, Travers K, Wyrwich KW, Svedsäter H, Locklear J, Mattera MS, et al. Humanistic and economic burden of generalized anxiety disorder in North America and Europe. J Affect Disord. 2012 Oct;140(2):103–12.

4. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593–602.

5. Wittchen H-U, Kessler RC, Beesdo K, Krause P, Höfler M, Hoyer J. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry. 2002;63 Suppl 8:24–34.

6. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014 May;28(5):403–39.

7. Wolgensinger L. Cognitive behavioral group therapy for anxiety: recent developments. Dialogues Clin Neurosci. 2015 Sep;17(3):347–51.

8. Caruso R, Grassi L, Biancosino B, Marmai L, Bonatti L, Moscara M, et al. Exploration of experiences in therapeutic groups for patients with severe mental illness: development of the Ferrara group experiences scale (FE- GES). BMC Psychiatry. 2013 Dec;13(1):242.

9. Lemes CB, Neto JO. Aplicações da psicoeducação no contexto da saúde. Temas Psicol. 2017;25(1):17–28.

10. Jensen PS, Weersing R, Hoagwood KE, Goldman E. What is the evidence for evidence-based treatments? A hard look at our soft underbelly. Ment Health Serv Res. 2005 Mar;7(1):53–74.

11. Baldwin SA, Wampold BE, Imel ZE. Untangling the alliance-outcome correlation: exploring the relative importance of therapist and patient variability in the alliance. J Consult Clin Psychol. 2007 Dec;75(6):842–52.

12. Kelley FA, Gelso CJ, Fuertes JN, Marmarosh C, Lanier SH. The Real Relationship Inventory: Development and psychometric investigation of the client form. Psychotherapy: Theory, Research, Practice, Training. 2010;47(4):540–53.

13. Costa MA, Gonçalves FG, Tatton-Ramos T, Fonseca NKOD, Schwinn JK, Alves SG, et al. A Three-Arm Randomized Clinical Trial Comparing The Efficacy Of A Mindfulness-Based Intervention With An Active Comparison Group And Fluoxetine Treatment For Adults With Generalized Anxiety Disorder. Psychother Psychosom. 2020 Dec 15:1-11.

14. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.

15. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092–7.

16. Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). Depress Anxiety. 2001;13(4):166–78.

17. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida "WHOQOL-bref". Rev Saúde Pública. 2000 Apr;34(2):178–83.

18. Beck JG, Stanley M, Zebb B. Psychometric properties of the Penn State Worry Questionnaire in older adults. Journal of Clinical Geropsychology. 1995 Jan 1;1:33–42.

19. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the penn state worry questionnaire. Behav Res Ther. 1990;28(6):487–95.

20. Castillo C, Macrini L, Cheniaux E, Landeira-Fernandez J. Psychometric properties and latent structure of the Portuguese version of the Penn State Worry Questionnaire. Span J Psychol. 2010 May;13(1):431–43.

21. Guy W. Clinical Global Impressions CGI. In: ECDEU Assessment Manual for Psychopharmacology. National Institute of Mental Health: Review Edition; 1976.

22. Dugas MJ, Ladouceur R, Léger E, Freeston MH, Langlois F, Provencher MD, et al. Group cognitive-behavioral therapy for generalized anxiety disorder: treatment outcome and long-term follow-up. J Consult Clin Psychol. 2003 Aug;71(4):821–5.

23. Leahy RL. Livre de ansiedade. Porto Alegre: Artmed; 2011.

24. Vorspan F, Mehtelli W, Dupuy G, Bloch V, Lépine J-P. Anxiety and substance use disorders: co-occurrence and clinical issues. Curr Psychiatry Rep. 2015 Feb;17(2):4.

25. Passos GS, Tufik S, Santana MG de, Poyares D, Mello MT de. [Nonpharmacologic treatment of chronic insomnia]. Braz J Psychiatry. 2007 Sep;29(3):279–82.

26. Carek PJ, Laibstain SE, Carek SM. Exercise for the Treatment of Depression and Anxiety. Int J Psychiatry Med. 2011 Jan;41(1):15–28.

27. Finger, I, Oliveira M da S. A prática da terapia cognitivo-comportamental nos transtornos alimentares e obesidade. Novo Hamburgo: Sinopys; 2016.

28. Fogarty C, Hevey D, McCarthy O. Effectiveness of cognitive behavioural group therapy for social anxiety disorder: long-term benefits and aftercare. Behav Cogn Psychother. 2019 Sep;47(5):501–13.

29. Holas P, Suszek H, Szaniawska M, Kokoszka A. Group Cognitive-Behavioral Therapy for Anxiety Disorders With Personality Disorders in Day Clinic Setting. Perspect Psychiatr Care. 2016 Jul;52(3):186–93.

30. Kodal A, Fjermestad K, Bjelland I, Gjestad R, Öst L-G, Bjaastad JF, et al. Long-term effectiveness of cognitive behavioral therapy for youth with anxiety disorders. J Anxiety Disord. 2018 Jan;53:58–67.

31. Bilet T, Olsen T, Andersen JR, Martinsen EW. Cognitive behavioral group therapy for panic disorder in a general clinical setting: a prospective cohort study with 12 to 31-years follow-up. BMC Psychiatry. 2020 May 24;20(1):259.

32. Norton PJ, Barrera TL. Transdiagnostic versus diagnosis-specific cbt for anxiety disorders: a preliminary randomized controlled noninferiority trial. Depress Anxiety. 2012 Oct;29(10):874–82.

33. Hui C, Zhihui Y. Group cognitive behavioral therapy targeting intolerance of uncertainty: a randomized trial for older Chinese adults with generalized anxiety disorder. Aging Ment Health. 2017 Dec;21(12):1294–302.

34. Evans S, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. J Anxiety Disord. 2008 May;22(4):716–21.

35. Hoge EA, Bui E, Marques L, Metcalf CA, Morris LK, Robinaugh DJ, et al. Randomized Controlled Trial of Mindfulness Meditation for Generalized Anxiety Disorder: Effects on Anxiety and Stress Reactivity. J Clin Psychiatry. 2013 Aug 15;74(08):786–92.

36. Yuan M, Zhu H, Qiu C, Meng Y, Zhang Y, Shang J, et al. Group cognitive behavioral therapy modulates the resting-state functional connectivity of amygdala-related network in patients with generalized social anxiety disorder. BMC Psychiatry. 2016 Jun 13;16:198.

37. Barlow SH, Burlingame GM. Essential theory, processes, and procedures for successful group psychotherapy: Group cohesion as exemplar. J Contemp Psychother. 2006 Sep;36(3):107–12.

38. Bernard H, Burlingame G, Flores P, Greene L, Joyce A, Kobos JC, et al. Clinical Practice Guidelines for Group Psychotherapy. Int J Group Psychother. 2008 Oct;58(4):455–542.

39. Caruso R, Grassi L, Biancosino B, Marmai L, Bonatti L, Moscara M, et al. Exploration of experiences in therapeutic groups for patients with severe mental illness: development of the Ferrara group experiences scale (FE- GES). BMC Psychiatry. 2013 Dec;13(1):242.

40. Burlingame GM, McClendon DT, Yang C. Cohesion in group therapy: A meta-analysis. Psychotherapy (Chic). 2018 Dec;55(4):384–98.

41. Gullo S, Lo Coco G, Di Fratello C, Giannone F, Mannino G, Burlingame G. Group climate, cohesion and curative climate. A study on the common factors in group process and their relation with members attachment dimensions. ResPsy [Internet]. 2015 Mar 11 [cited 2021 Apr 11];18(1). Available from: https://www.researchinpsychotherapy.org/index.php/rpsy/article/view/160

42. Marziali E, Munroe-Blum H, McCleary L. The contribution of group cohesion and group alliance to the outcome of group psychotherapy. Int J Group Psychother. 1997 Oct;47(4):475–97.

43. Tasca GA, Cabrera C, Kristjansson E, MacNair-Semands R, Joyce AS, Ogrodniczuk JS. The therapeutic factor inventory-8: Using item response theory to create a brief scale for continuous process monitoring for group psychotherapy. Psychotherapy Research. 2016 Mar 3;26(2):131–45.

44. Stringer B, Van Meijel B, De Vree W, Van der Bijl J. User involvement in mental health care: the role of nurses. A literature review. J Psychiatr Ment Health Nurs. 2008 Oct;15(8):678–83.

45. Fraser C, Grundy A, Meade O, Callaghan P, Lovell K. EQUIP training the trainers: an evaluation of a training programme for service users and carers involved in training mental health professionals in user-involved care planning. J Psychiatr Ment Health Nurs. 2017 Aug;24(6):367–76.

46. Happell B, Byrne L, McAllister M, Lampshire D, Roper C, Gaskin CJ, et al. Consumer involvement in the tertiary-level education of mental health professionals: a systematic review. Int J Ment Health Nurs. 2014 Feb;23(1):3–16.

15 CONSIDERAÇÕES FINAIS

O TAG se apresenta como um transtorno de alta prevalência, crônico, com curso flutuante e taxa de remissão completa baixa (7). O transtorno está associado a um prejuízo funcional, comorbidades médicas (100,13) e VFC reduzida (42,251). Junto a isto, a presença de um viés atencional relacionado a possíveis interpretações de ameaças e uma desregulação emocional estão relacionados a etiologia e manutenção do transtorno (58).

Dito isto, a presente tese apresenta dados clinicamente relevantes através da atenção voltada para melhor elucidação dos processos cognitivos, emocionais e biológicos implicados no TAG. Considerando que o TAG ainda é um transtorno subdiagnosticado e menos de um terço dos pacientes são devidamente tratados (7,106), espera-se destacar com os presentes achados a importância de investigar tratamentos eficazes para reduzir as falhas de processamento cognitivo e a desregulação emocional em conjunto com a redução dos sintomas de ansiedade. Afinal, diminuir a latência entre o diagnóstico e tratamento do TAG, aumentaria a possibilidades de intervenções precoces e ofertaria intervenções terapêuticas focadas nos sintomas essenciais do transtorno em questão.

Sendo assim, artigo 1 da presente tese apresenta a relação entre a VFC e a regulação emocional em pacientes com TAG. As mudanças da VFC do repouso para a tarefa aparecem como um preditor de melhora da interferência emocional em pacientes com TAG. A variação da VFC do basal para o repouso prediz melhora na El no grupo FLX em comparação ao grupo QV, o que estava de acordo com a nossa hipótese, mas que não ocorreu no Mindfulness. Nossos resultados apoiam estudos prévios afirmando que a VFC em repouso é um marcador autonômico da capacidade de regulação emocional. O achado evidencia a capacidade de regulação emocional por meio da flexibilidade autonômica. Resultados desse estudo contribuem para o entendimento de um processamento desadaptativo de um estímulo emocional observado em indivíduos com a VFC reduzida, o que pode ser prejudicial à saúde física e emocional e que explica uma variedade de psicopatologias e questões de saúde. Por outro lado, uma alta VFC está relacionada à um bom ajustamento e melhora de processos cognitivos e emocionais conforme resultado encontrado no grupo FLX.

O artigo 2 aborda os efeitos dos diferentes tratamentos sob os processos atencionais e emocionais em pacientes com TAG. O possível papel da valência emocional e relevância social dos estímulos na modulação da atenção pode ser relevante para explorar à influência da atenção sob dificuldades de controle e inibição.

Os achados apontam que as três intervenções terapêuticas (mindfulness, QV e FLX) melhoram o desempenho cognitivo e podem modificar o processamento cognitivo, emocional e reações comportamentais frente a estímulos emocionais de maneiras diferentes. O grupo mindfulness apresentou um aumento significativo no número de acertos em estímulos emocionais após o tratamento em comparação ao baseline. O grupo FLX foi o único a demonstrar uma redução significativa da interferência emocional. E, por fim, o grupo FLX e o controle ativo se mostraram eficazes para redução do tempo de respostas e melhora atencional na tarefa cognitiva.

O artigo 3 aponta para um aspecto importante que é o estilo e a qualidade de vida dos pacientes com TAG. Através da aplicação de um protocolo de qualidade de vida de 8 semanas, evidencia-se a redução significativa da ansiedade e a melhora da qualidade de vida dos pacientes acometidos pelo transtorno. Ainda que se faça necessário um aprimoramento do protocolo visando uma melhora na manutenção dos ganhos e menores taxas de abandono, o protocolo se mostra como uma opção viável e eficaz para a redução de sintomas de ansiedade e desenvolvimento de hábitos de vida saudáveis.

O presente estudo fornece dados de como futuras pesquisas podem ser projetadas em direção a neurociência e tratamentos psicossociais personalizados para os transtornos de ansiedade. Os resultados do ensaio clinico randomizado caminham para a orientação da intervenção terapêutica no processamento do TAG, relações entre níveis de análise (isto é, cognitiva, emocional ou neural), e o mais importante, apresentam preditores de resultados terapêuticos.

Embora mais pesquisas sejam necessárias, os efeitos dos tratamentos sob o controle atencional e a interferência emocional em pacientes com TAG podem ser úteis no planejamento de estratégias ideais para redução dos déficits atencionais e emocionais presentes no transtorno. Junto à isto, a utilização de medidas comportamentais e fisiológicas de processamento de informações emocionais forneceu um quadro mais completo da relação da VFC com o processamento afetivo, oferecendo suporte para compreender constructos biocomportamentais relevantes para a saúde mental.

Finalmente, o protocolo de qualidade de vida se apresenta como um tratamento eficaz para a redução de ansiedade e melhora de estratégias cognitivas e comportamentais e oferta o acesso à um tratamento psicológico acessível aos indivíduos com TAG com ganhos mantidos ao longo do tempo.

REFERÊNCIAS

1. Cloninger CR. A unified biosocial theory of personality and its role in the development of anxiety states: a reply to commentaries. Psychiatr Dev. 1988;6(2):83–120.

2. Harrigan JA, Wilson K, Rosenthal R. Detecting state and trait anxiety from auditory and visual cues: a meta-analysis. Pers Soc Psychol Bull. 2004 Jan;30(1):56–66.

3. Borkovec TD, Alcaine OM, Behar E. Avoidance theory of worry and generalized anxiety disorder. In: Generalized anxiety disorder: advances in research and practice. New York: Guilford Press; 2004. p. 77–108.

4. Pitta JCN. Como diagnosticar e tratar transtornos de ansiedade. Rev Med. 2011;68(12):6–13.

5. Ströhle A, Gensichen J, Domschke K. The Diagnosis and Treatment of Anxiety Disorders. Dtsch Arztebl Int [Internet]. 2018 Sep 14 [cited 2021 Fev 16]; Available from: https://www.aerzteblatt.de/10.3238/arztebl.2018.0611

6. Gottschalk MG, Domschke K. Novel developments in genetic and epigenetic mechanisms of anxiety: Current Opinion in Psychiatry. 2016 Jan;29(1):32–8.

7. American Psychiatric Association. DSM-5: manual diagnóstico e estatístico de transtornos mentais. 5. ed. Porto Alegre: Artmed; 2014. 992 p.

8. Daitch C, Lorberbaum, L. Anxious in love: How to manage your anxiety, reduce conflict, and reconnect with your partner. Oakland: New Harbinger; 2012.

9. Fisher AJ, Newman MG. Heart rate and autonomic response to stress after experimental induction of worry versus relaxation in healthy, high-worry, and generalized anxiety disorder individuals. Biol Psychol. 2013 Apr;93(1):65–74.

10. Kemp AH, Brunoni AR, Santos IS, Nunes MA, Dantas EM, Carvalho de Figueiredo R, et al. Effects of Depression, Anxiety, Comorbidity, and Antidepressants on Resting-State Heart Rate and Its Variability: An ELSA-Brasil Cohort Baseline Study. AJP. 2014 Dec;171(12):1328–34.

11. Grenier S, Préville M, Boyer R, O'Connor K, Béland S-G, Potvin O, et al. The impact of DSM-IV symptom and clinical significance criteria on the prevalence estimates of subthreshold and threshold anxiety in the older adult population. Am J Geriatr Psychiatry. 2011 Apr;19(4):316–26.

12. Craske MG, Stein MB, Eley TC, Milad MR, Holmes A, Rapee RM, et al. Anxiety disorders. Nat Rev Dis Primers. 2017 Dec 21;3(1):17024.

13. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593–602.

14. Ruscio AM, Hallion LS, Lim CCW, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, et al. Cross-sectional Comparison of the Epidemiology of *DSM-5* Generalized Anxiety Disorder Across the Globe. JAMA Psychiatry. 2017 May 1;74(5):465.

15. Ruscio AM, Hallion LS, Lim CCW, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, et al. Cross-sectional Comparison of the Epidemiology of *DSM-5* Generalized Anxiety Disorder Across the Globe. JAMA Psychiatry. 2017 May 1;74(5):465.

16. Fogarty CT, Sharma S, Chetty VK, Culpepper L. Mental health conditions are associated with increased health care utilization among urban family medicine patients. J Am Board Fam Med. 2008 Oct;21(5):398–407.

17. Hoffman DL, Dukes EM, Wittchen H-U. Human and economic burden of generalized anxiety disorder. Depress Anxiety. 2008;25(1):72–90.

18. Newman MG. Recommendations for a cost-offset model of psychotherapy allocation using generalized anxiety disorder as an example. J Consult Clin Psychol. 2000 Aug;68(4):549–55.

19. Tully PJ, Cosh SM. Generalized anxiety disorder prevalence and comorbidity with depression in coronary heart disease: a meta-analysis. J Health Psychol. 2013 Dec;18(12):1601–16.

20. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. Medical Journal of Australia [Internet]. 2009 Apr [cited 2021 Feb 15];190(S7). Available from: https://onlinelibrary.wiley.com/doi/abs/10.5694/j.1326-5377.2009.tb02471.x

21. Solano JP, Gomes B, Higginson IJ. A Comparison of Symptom Prevalence in Far Advanced Cancer, AIDS, Heart Disease, Chronic Obstructive Pulmonary Disease and Renal Disease. J Pain Symptom Manage. 2006 Jan;31(1):58–69.

22. Janssen D, Spruit M, Wouters E, Schols J. Daily symptom burden in end-stage chronic organ failure: a systematic review. Palliat Med. 2008 Dec;22(8):938–48.

23. Mennin DS, Heimberg RG, Turk CL, Fresco DM. Preliminary evidence for an emotion dysregulation model of generalized anxiety disorder. Behav Res Ther. 2005 Out;43(10):1281–310.

24. Borkovec TD, Alcaine, OM, Behar E. Avoidance theory of worry and generalized anxiety disorder. In: Generalized anxiety disorder: advances in research and practice. New York: Guilford Press; 2004. p. 77–108.

25. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biol Psychiatry. 1996 Feb 15;39(4):255–66.

26. Skinner BF. Two Types of Conditioned Reflex: A Reply to Konorski and Miller. J Gen Psychol. 1937 Jan;16(1):272–9.

27. Lee S, Kim S-J, Kwon O-B, Lee JH, Kim J-H. Inhibitory networks of the amygdala for emotional memory. Front Neural Circuits. 2013;7:129.

28. Maren S. Neurobiology of Pavlovian fear conditioning. Annu Rev Neurosci. 2001;24:897–931.

29. Lee S, Kim S-J, Kwon O-B, Lee JH, Kim J-H. Inhibitory networks of the amygdala for emotional memory. Front Neural Circuits. 2013;7:129.

30. MacNamara A, Proudfit GH. Cognitive load and emotional processing in generalized anxiety disorder: Electrocortical evidence for increased distractibility. J Abnorm Psychol. 2014 Aug;123(3):557–65.

31. Mennin DS, Heimberg RG, Turk CL, Fresco DM. Preliminary evidence for an emotion dysregulation model of generalized anxiety disorder. Behav Res Ther. 2005 Oct;43(10):1281–310.

32. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015 Sep;17(3):327–35.

33. Kumar V, Bhat ZA, Kumar D. Animal models of anxiety: a comprehensive review. J Pharmacol Toxicol Methods. 2013 Oct;68(2):175–83.

34. Pessoa L, Japee S, Sturman D, Ungerleider LG. Target Visibility and Visual Awareness Modulate Amygdala Responses to Fearful Faces. Cerebral Cortex. 2006 Mar 1;16(3):366–75.

35. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000 Dec;61(3):201–16.

36. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010 May;141(2):122–31.

37. Vogelzangs N, Seldenrijk A, Beekman ATF, van Hout HPJ, de Jonge P, Penninx BWJH. Cardiovascular disease in persons with depressive and anxiety disorders. J Affect Disord. 2010 Sep;125(1–3):241–8.

38. Chalmers JA, Quintana DS, Abbott MJ-A, Kemp AH. Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. Front Psychiatry [Internet]. 2014 Jul 18 [cited 2020 Nov 8];5. Available from: http://journal.frontiersin.org/article/10.3389/fpsyt.2014.00080/abstract

39. Kemp AH, Brunoni AR, Santos IS, Nunes MA, Dantas EM, Carvalho de Figueiredo R, et al. Effects of Depression, Anxiety, Comorbidity, and Antidepressants on Resting-State Heart Rate and Its Variability: An ELSA-Brasil Cohort Baseline Study. AJP. 2014 Dec;171(12):1328–34.

40. Shinba T. Major depressive disorder and generalized anxiety disorder show different autonomic dysregulations revealed by heart-rate variability analysis in first-onset drug-naïve patients without comorbidity: HRV in depression and anxiety. Psychiatry Clin Neurosci. 2017 Feb;71(2):135–45.

41. Shah AJ, Lampert R, Goldberg J, Veledar E, Bremner JD, Vaccarino V. Posttraumatic Stress Disorder and Impaired Autonomic Modulation in Male Twins. Biol Psychiatry. 2013 Jun;73(11):1103–10.

42. Chang H-A, Chang C-C, Tzeng N-S, Kuo TBJ, Lu R-B, Huang S-Y. Generalized Anxiety Disorder, Comorbid Major Depression and Heart Rate Variability: A Case-Control Study in Taiwan. Psychiatry Investig. 2013;10(4):326.

43. Levine JC, Fleming R, Piedmont JI, Cain SM, Chen W-J. Heart rate variability and generalized anxiety disorder during laboratory-induced worry and aversive imagery. J Affect Disord. 2016 Nov;205:207–15.

44. Strawn JR, Wehry AM, Chu W-J, Adler CM, Eliassen JC, Cerullo MA, et al. Neuroanatomic abnormalities in adolescents with generalized anxiety disorder: a voxel-based morphometry study. Depress Anxiety. 2013 Sep;30(9):842–8.

45. Tromp DPM, Grupe DW, Oathes DJ, McFarlin DR, Hernandez PJ, Kral TRA, et al. Reduced Structural Connectivity of a Major Frontolimbic Pathway in Generalized Anxiety Disorder. Arch Gen Psychiatry. 2012 Sep 1;69(9):925.

46. Mohlman J, Price RB, Eldreth DA, Chazin D, Glover DM, Kates WR. The relation of worry to prefrontal cortex volume in older adults with and without generalized anxiety disorder. Psychiatry Res. 2009 Aug 30;173(2):121–7.

47. Price RB, Eldreth DA, Mohlman J. Deficient prefrontal attentional control in late-life generalized anxiety disorder: an fMRI investigation. Transl Psychiatry. 2011 Oct;1(10):e46–e46.

48. Roy AK, Fudge JL, Kelly C, Perry JSA, Daniele T, Carlisi C, et al. Intrinsic Functional Connectivity of Amygdala-Based Networks in Adolescent Generalized Anxiety Disorder. J Am Acad Child Adolesc Psychiatry. 2013 Mar;52(3):290-299.e2.

49. Abdallah CG, Coplan JD, Jackowski A, Sato JR, Mao X, Shungu DC, et al. A pilot study of hippocampal volume and N-acetylaspartate (NAA) as response biomarkers in riluzole-treated patients with GAD. European Neuropsychopharmacology. 2013 Apr;23(4):276–84.

50. De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Dahl RE, Axelson DA, et al. Superior temporal gyrus volumes in pediatric generalized anxiety disorder. Biol Psychiatry. 2002 Apr 1;51(7):553–62.

51. Hettema JM, Kettenmann B, Ahluwalia V, McCarthy C, Kates WR, Schmitt JE, et al. Pilot multimodal twin imaging study of generalized anxiety disorder: Twin GAD MRI. Depress Anxiety. 2012 Mar;29(3):202–9.

52. Segerstrom SC, Stanton AL, Alden LE, Shortridge BE. A Multidimensional Structure for Repetitive Thought: What's on Your Mind, and How, and How Much? J Pers Soc Psychol. 2003;85(5):909–21.

53. Mathew SJ, Mao X, Coplan JD, Smith ELP, Sackeim HA, Gorman JM, et al. Dorsolateral prefrontal cortical pathology in generalized anxiety disorder: a proton

magnetic resonance spectroscopic imaging study. Am J Psychiatry. 2004 Jun;161(6):1119–21.

54. Beck AT. Cognitive therapy and emotion disorders. New York: International Universities Press; 1976.

55. Eysenck MW. Anxiety: the cognitive perspective. England: Psychology press; 1992.

56. Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. Am Psychol. 2000 Nov;55(11):1247–63.

57. Pessoa L. How do emotion and motivation direct executive control? Trends Cogn Sci. 2009 Apr;13(4):160–6.

58. Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IJzendoorn MH. Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. Psychol Bull. 2007;133(1):1–24.

59. Langner R, Eickhoff SB. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. Psychol Bull. 2013 Jul;139(4):870–900.

60. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: Attentional control theory. Emotion. 2007;7(2):336–53.

61. Forster S, Nunez Elizalde AO, Castle E, Bishop SJ. Unraveling the Anxious Mind: Anxiety, Worry, and Frontal Engagement in Sustained Attention Versus Off-Task Processing. Cerebral Cortex. 2015 Mar 1;25(3):609–18.

62. Wright L, Lipszyc J, Dupuis A, Thayapararajah SW, Schachar R. Response inhibition and psychopathology: a meta-analysis of go/no-go task performance. J Abnorm Psychol. 2014 May;123(2):429–39.

63. Derryberry D, Reed MA. Anxiety-related attentional biases and their regulation by attentional control. J Abnorm Psychol. 2002 May;111(2):225–36.

64. Grillon C, Robinson OJ, Mathur A, Ernst M. Effect of attention control on sustained attention during induced anxiety. Cognition and Emotion. 2016 May 18;30(4):700–12.

65. Bar-Haim Y. Research review: Attention bias modification (ABM): a novel treatment for anxiety disorders. J Child Psychol Psychiatry. 2010 Aug;51(8):859–70.

66. Bandelow B, Lichte T, Rudolf S, Wiltink J, Beutel ME. The German guidelines for the treatment of anxiety disorders. Eur Arch Psychiatry Clin Neurosci. 2015 Aug;265(5):363–73.

67. Wilson H, Mannix S, Oko-osi H, Revicki DA. The Impact of Medication on Health-Related Quality of Life in Patients with Generalized Anxiety Disorder. CNS Drugs. 2015 Jan;29(1):29–40.

68. Nemeroff CB. Anxiolytics: past, present, and future agents. J Clin Psychiatry. 2003;64 Suppl 3:3–6.

69. Kent JM, Coplan JD, Gorman JM. Clinical utility of the selective serotonin reuptake inhibitors in the spectrum of anxiety. Biol Psychiatry. 1998 Nov 1;44(9):812–24.

70. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. J Clin Psychiatry. 2010 Jul;71(7):839–54.

71. Reinhold JA, Rickels K. Pharmacological treatment for generalized anxiety disorder in adults: an update. Expert Opin Pharmacother. 2015;16(11):1669–81.

72. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019 Fev 23;393(10173):768–77.

73. Kapczinski F, dos Santos Souza JJ, Batista Miralha da Cunha AA, Schmitt RR. Antidepressants for generalised anxiety disorder (GAD). In: Cochrane Collaboration, organizator. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2003 [cited 2021 Feb 15]. p. CD003592. Available from: http://doi.wiley.com/10.1002/14651858.CD003592

74. Shinfuku M, Kishimoto T, Uchida H, Suzuki T, Mimura M, Kikuchi T. Effectiveness and safety of long-term benzodiazepine use in anxiety disorders: a systematic review and meta-analysis. Int Clin Psychopharmacol. 2019 Sep;34(5):211–21.

75. Borkovec TD, Costello E. Efficacy of Applied Relaxation and Cognitive–Behavioral Therapy in the Treatment of Generalized Anxiety Disorder. J Consult Clin Psychol. 1993 Sep 1;61:611–9.

76. Littlejohns P, Leng G, Culyer T, Drummond M. NICE clinical guidelines: Maybe health economists should participate in guideline development. BMJ. 2004 Sep 2;329(7465):571.

77. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. Cogn Ther Res. 2012 Oct;36(5):427–40.

78. Hall J, Kellett S, Berrios R, Bains MK, Scott S. Efficacy of Cognitive Behavioral Therapy for Generalized Anxiety Disorder in Older Adults: Systematic Review, Meta-Analysis, and Meta-Regression. The American Journal of Geriatric Psychiatry. novembro de 2016;24(11):1063–73.

79. Daitch C. Anxiety disorders: The go-to guide for clients and therapists (go-to guides for mental health). New York: WW Norton & Company; 2011.

80. Russell T. Body in mind training: mindful movement for severe and enduring mental illness. British Journal of Wellbeing. 2011 Apr;2(4):13–6.

81. Baker AW, Frumkin MR, Hoeppner SS, LeBlanc NJ, Bui E, Hofmann SG, et al. Facets of Mindfulness in Adults with Generalized Anxiety Disorder and Impact of Co-occurring Depression. Mindfulness. 2019 May;10(5):903–12.

82. Hoge EA, Bui E, Palitz SA, Schwarz NR, Owens ME, Johnston JM, et al. The effect of mindfulness meditation training on biological acute stress responses in generalized anxiety disorder. Psychiatry Research. 2018 Apr;262:328–32.

83. Kozasa EH, Sato JR, Lacerda SS, Barreiros MAM, Radvany J, Russell TA, et al. Meditation training increases brain efficiency in an attention task. NeuroImage. 2012 Jan;59(1):745–9.

84. Alladin, A. Integrative CBT for anxiety disorders: An evidence-based approach to enhancing cognitive behavioural therapy with mindfulness and hypnotherapy. Chichester, UK: Willey Blackwell; 2016.

85. Evans S, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. J Anxiety Disord. 2008 May;22(4):716–21.

86. Roemer L, Orsillo SM. An Open Trial of an Acceptance-Based Behavior Therapy for Generalized Anxiety Disorder. Behavior Therapy. 2007 Mar;38(1):72–85.

87. Daitch C. Cognitive Behavioral Therapy, Mindfulness, and Hypnosis as Treatment Methods for Generalized Anxiety Disorder. Am J Clin Hypn. 2018 Jul 9;61(1):57–69.

88. Pitta, J.C.N. Como diagnosticar e tratar transtornos de ansiedade. Rev. med. 2011;68(12):6–13.

89. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biol Psychiatry. 1996 Feb 15;39(4):255–66.

90. Skinner BF. Ciência e comportamento humano. UNB/FUNBEC; 1970.

91. Bishop SJ. Neural Mechanisms Underlying Selective Attention to Threat. Annals of the New York Academy of Sciences. 2008 May;1129(1):141–52.

92. Skinner BF. Two Types of Conditioned Reflex: A Reply to Konorski and Miller. J Gen Psychol. 1937 Jan;16(1):272–9.

93. Dunsmoor JE, Paz R. Fear Generalization and Anxiety: Behavioral and Neural Mechanisms. Biological Psychiatry. 2015 Sep;78(5):336–43.

94. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med. 2013 May;43(5):897–910.

95. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14(Suppl 1):S1.

96. Wittchen H-U, Kessler RC, Beesdo K, Krause P, Höfler M, Hoyer J. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry. 2002;63 Suppl 8:24–34.

97. Wittchen H-U, Kessler RC, Beesdo K, Krause P, Höfler M, Hoyer J. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry. 2002;63 Suppl 8:24–34.

98. Kessler RC, Gruber M, Hettema JM, Hwang I, Sampson N, Yonkers KA. Co-morbid major depression and generalized anxiety disorders in the National Comorbidity Survey follow-up. Psychol Med. 2008 Mar;38(3):365–74.

99. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun 1;62(6):593.

100. Comer JS, Blanco C, Hasin DS, Liu S-M, Grant BF, Turner JB, et al. Health-related quality of life across the anxiety disorders: results from the national epidemiologic survey on alcohol and related conditions (NESARC). J Clin Psychiatry. 2011 Jan;72(1):43–50.

101. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011 Sep;21(9):655–79.

102. Kanwar A, Malik S, Prokop LJ, Sim LA, Feldstein D, Wang Z, et al. The association between anxiety disorders and suicidal behaviors: a systematic review and meta-analysis. Depress Anxiety. 2013 Oct;30(10):917–29.

103. Barger SD, Sydeman SJ. Does generalized anxiety disorder predict coronary heart disease risk factors independently of major depressive disorder? J Affect Disord. 2005 Sep;88(1):87–91.

104. Beesdo K, Hoyer J, Jacobi F, Low NCP, Höfler M, Wittchen H-U. Association between generalized anxiety levels and pain in a community sample: Evidence for diagnostic specificity. J Anxiety Disord. 2009 Jun;23(5):684–93.

105. Martens EJ, de Jonge P, Na B, Cohen BE, Lett H, Whooley MA. Scared to Death? Generalized Anxiety Disorder and Cardiovascular Events in Patients With Stable Coronary Heart Disease: The Heart and Soul Study. Arch Gen Psychiatry. 2010 Jun 1;67(7):750.

106. Baldwin DS, Allgulander C, Bandelow B, Ferre F, Pallanti S. An international survey of reported prescribing practice in the treatment of patients with generalised anxiety disorder. World J Biol Psychiatry. 2012 Oct;13(7):510–6.

107. Wilson H, Mannix S, Oko-osi H, Revicki DA. The Impact of Medication on Health-Related Quality of Life in Patients with Generalized Anxiety Disorder. CNS Drugs. 2015 Jan;29(1):29–40.

108. Cuijpers P, Sijbrandij M, Koole S, Huibers M, Berking M, Andersson G. Psychological treatment of generalized anxiety disorder: a meta-analysis. Clin Psychol Rev. 2014 Mar;34(2):130–40.

109. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: Attentional control theory. Emotion. 2007;7(2):336–53.

110. Deschenes SS, Dugas MJ, Radomsky AS, Buhr K. Experimental Manipulation of Beliefs about Uncertainty: Effects on Interpretive Processing and Access to Threat Schemata. Journal of Experimental Psychopathology. 2010 Jan;1(1):jep.008510.

111. Mennin DS, Fresco DM. What, Me Worry and Ruminate About *DSM-5* and RDoC? The Importance of Targeting Negative Self-Referential Processing. Clin Psychol Sci Pract. 2013 Sep;20(3):258–67.

112. Roemer L, Salters K, Raffa SD, Orsillo SM. Fear and Avoidance of Internal Experiences in GAD: Preliminary Tests of a Conceptual Model. Cogn Ther Res. 2005 Feb;29(1):71–88.

113. Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. Am Psychol. 2000 Nov;55(11):1247–63.

114. Wells A. A Cognitive Model of Generalized Anxiety Disorder. Behav Modif. 1999 Oct;23(4):526–55.

115. Watkins E. Appraisals and strategies associated with rumination and worry. Personality and Individual Differences. 2004 Sep;37(4):679–94.

116. Nolen-Hoeksema S. The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. J Abnorm Psychol. 2000 Aug;109(3):504–11.

117. Roemer L, Orsillo SM. An Open Trial of an Acceptance-Based Behavior Therapy for Generalized Anxiety Disorder. Behavior Therapy. 2007 Mar;38(1):72–85.

118. Derakshan N, Eysenck MW. Anxiety, Processing Efficiency, and Cognitive Performance: New Developments from Attentional Control Theory. European Psychologist. 2009 Jan;14(2):168–76.

119. Bandelow B, Baldwin D, Abelli M, Altamura C, Dell'Osso B, Domschke K, et al. Biological markers for anxiety disorders, OCD and PTSD – a consensus statement. Part I: Neuroimaging and genetics. World J Biol Psychiatry. 2016 Jul 3;17(5):321–65.

120. Mather L, Blom V, Bergström G, Svedberg P. An Underlying Common Factor, Influenced by Genetics and Unique Environment, Explains the Covariation Between Major Depressive Disorder, Generalized Anxiety Disorder, and Burnout: A Swedish Twin Study. Twin Res Hum Genet. 2016 Dez;19(6):619–27.

121. Porta-Casteràs D, Fullana MA, Tinoco D, Martínez-Zalacaín I, Pujol J, Palao DJ, et al. Prefrontal-amygdala connectivity in trait anxiety and generalized anxiety disorder: Testing the boundaries between healthy and pathological worries. J Affect Disord. 2020 Apr 15;267:211–9.

122. MacNamara A, Proudfit GH. Cognitive load and emotional processing in generalized anxiety disorder: Electrocortical evidence for increased distractibility. J Abnorm Psychol. 2014 Aug;123(3):557–65.

123. Park G, Thayer JF. From the heart to the mind: cardiac vagal tone modulates top-down and bottom-up visual perception and attention to emotional stimuli. Front Psychol

[Internet]. 2014 May 1 [cited 2020 Nov 7];5. Available from: http://journal.frontiersin.org/article/10.3389/fpsyg.2014.00278/abstract

124. Shechner T, Jarcho JM, Wong S, Leibenluft E, Pine DS, Nelson EE. Threats, rewards, and attention deployment in anxious youth and adults: An eye tracking study. Biological Psychology. 2017 Jan;122:121–9.

125. Wiers RW, Teachman BA, De Houwer J. Implicit cognitive processes in psychopathology: an introduction. J Behav Ther Exp Psychiatry. 2007 Jun;38(2):95–104.

126. Tromp DPM, Grupe DW, Oathes DJ, McFarlin DR, Hernandez PJ, Kral TRA, et al. Reduced Structural Connectivity of a Major Frontolimbic Pathway in Generalized Anxiety Disorder. Arch Gen Psychiatry. 2012 Sep 1;69(9):925.

127. Amso D, Scerif G. The attentive brain: insights from developmental cognitive neuroscience. Nat Rev Neurosci. 2015 Out;16(10):606–19.

128. Banich MT. Executive Function: The Search for an Integrated Account. Curr Dir Psychol Sci. 2009 Apr;18(2):89–94.

129. Kalanthroff E, Henik A, Derakshan N, Usher M. Anxiety, emotional distraction, and attentional control in the Stroop task. Emotion. 2016 Apr;16(3):293–300.

130. Hart SJ, Green SR, Casp M, Belger A. Emotional priming effects during Stroop task performance. NeuroImage. 2010 Feb;49(3):2662–70.

131. Cohen N, Henik A, Mor N. Can emotion modulate attention? Evidence for reciprocal links in the attentional network test. Exp Psychol. 2011;58(3):171–9.

132. Kanske P. On the Influence of Emotion on Conflict Processing. Front Integr Neurosci [Internet]. 2012 [cited 2020 Dec 6];6. Available from: http://journal.frontiersin.org/article/10.3389/fnint.2012.00042/abstract

133. Ernst M, Lago T, Davis A, Grillon C. The effects of methylphenidate and propranolol on the interplay between induced-anxiety and working memory. Psychopharmacology. 2016 Oct;233(19–20):3565–74.

134. Vytal K, Cornwell B, Arkin N, Grillon C. Describing the interplay between anxiety and cognition: From impaired performance under low cognitive load to reduced anxiety under high load: Anxiety and cognition. Psychophysiol. 2012 Jun;49(6):842–52.

135. Clarke R, Johnstone T. Prefrontal inhibition of threat processing reduces working memory interference. Front Hum Neurosci [Internet]. 2013 [cited 2020 Dec 6];7. Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2013.00228/abstract

136. Kiyonaga A, Egner T. Working memory as internal attention: Toward an integrative account of internal and external selection processes. Psychon Bull Rev. 2013 Apr;20(2):228–42.

137. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration

Perspective on Self-regulation, Adaptation, and Health. ann behav med. 2009 Apr;37(2):141–53.

138. Mujica-Parodi LR, Korgaonkar M, Ravindranath B, Greenberg T, Tomasi D, Wagshul M, et al. Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. Hum Brain Mapp. 2009 Jan;30(1):47–58.

139. Taylor CB. Depression, heart rate related variables and cardiovascular disease. Int J Psychophysiol. 2010 Oct;78(1):80–8.

140. Gross JJ. Emotion regulation: Taking stock and moving forward. Emotion. 2013 Jun;13(3):359–65.

141. Krypotos A-M, Jahfari S, van Ast VA, Kindt M, Forstmann BU. Individual Differences in Heart Rate Variability Predict the Degree of Slowing during Response Inhibition and Initiation in the Presence of Emotional Stimuli. Front Psychology [Internet]. 2011 [cited 2020 Nov 11];2. Available from: http://journal.frontiersin.org/article/10.3389/fpsyg.2011.00278/abstract

142. Verbruggen F, Logan GD. Automatic and controlled response inhibition: Associative learning in the go/no-go and stop-signal paradigms. J Exp Psychol Gen. 2008;137(4):649–72.

143. Verbruggen F, Logan GD. Automatic and controlled response inhibition: Associative learning in the go/no-go and stop-signal paradigms. J Exp Psychol Gen. 2008;137(4):649–72.

144. De Houwer J, Tibboel H. Stop what you are not doing! Emotional pictures interfere with the task not to respond. Psychon Bull Rev. 2010 Out;17(5):699–703.

145. Bradley MM. Natural selective attention: Orienting and emotion. Psychophysiology. 2009 Jan;46(1):1–11.

146. Thigpen NN, Keil A, Freund AM. Responding to emotional scenes: effects of response outcome and picture repetition on reaction times and the late positive potential. Cognition and Emotion. 2018 Jan 2;32(1):24–36.

147. Vila J, Guerra P, Munoz M, Vico C, Viedmadeljesus M, Delgado L, et al. Cardiac defense: From attention to action. Int J Psychophysiol. 2007 Dec;66(3):169–82.

148. Haas SA, Amso D, Fox NA. The effects of emotion priming on visual search in socially anxious adults. Cognition and Emotion. 2017 Jul 4;31(5):1041–54.

149. LoBue V. More than just another face in the crowd: superior detection of threatening facial expressions in children and adults. Developmental Science. 2009 Mar;12(2):305–13.

150. Astudillo C, Muñoz K, Maldonado PE. Emotional Content Modulates Attentional Visual Orientation During Free Viewing of Natural Images. Front Hum Neurosci. 2018 Nov 15;12:459.

151. Oldrati V, Bardoni A, Poggi G, Urgesi C. Influence of Attention Control on Implicit and Explicit Emotion Processing of Face and Body: Evidence From Flanker and Same-or-Different Paradigms. Front Psychol. 2020 Jan 21;10:2971.

152. Bradley MM, Keil A, Lang PJ. Orienting and Emotional Perception: Facilitation, Attenuation, and Interference. Front Psychology [Internet]. 2012 [cited 2020 Nov 7];3. Available from: http://journal.frontiersin.org/article/10.3389/fpsyg.2012.00493/abstract

153. Grillon C, Robinson OJ, Mathur A, Ernst M. Effect of attention control on sustained attention during induced anxiety. Cognition and Emotion. 2016 May 18;30(4):700–12.

154. Wadlinger HA, Isaacowitz DM. Fixing our focus: training attention to regulate emotion. Pers Soc Psychol Rev. 2011 Fev;15(1):75–102.

155. Lutz A, Slagter HA, Dunne JD, Davidson RJ. Attention regulation and monitoring in meditation. Trends Cogn Sci. 2008 Apr;12(4):163–9.

156. Tang Y-Y, Posner MI. Attention training and attention state training. Trends Cogn Sci. 2009 May;13(5):222–7.

157. Menezes CB, de Paula Couto MC, Buratto LG, Erthal F, Pereira MG, Bizarro L. The Improvement of Emotion and Attention Regulation after a 6-Week Training of Focused Meditation: A Randomized Controlled Trial. Evid Based Complement Alternat Med. 2013;2013:1–11.

158. Slagter HA, Lutz A, Greischar LL, Francis AD, Nieuwenhuis S, Davis JM, et al. Mental Training Affects Distribution of Limited Brain Resources. In: Rugg MD, organizator. PLoS Biol. 2007 May 8;5(6):e138.

159. Teper R, Inzlicht M. Meditation, mindfulness and executive control: the importance of emotional acceptance and brain-based performance monitoring. Soc Cogn Affect Neurosci. 2013 Jan 1;8(1):85–92.

160. Chiesa A, Calati R, Serretti A. Does mindfulness training improve cognitive abilities? A systematic review of neuropsychological findings. Clin Psychol Rev. 2011 Apr;31(3):449–64.

161. Clark DA, Beck AT. Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. Trends Cogn Sci. 2010 Sep;14(9):418–24.

162. Van Bockstaele B, Verschuere B, Tibboel H, De Houwer J, Crombez G, Koster EHW. A review of current evidence for the causal impact of attentional bias on fear and anxiety. Psychological Bulletin. 2014 May;140(3):682–721.

163. Linehan, M. M. Treinamento de habilidades em DBT. 2. ed. Porto Alegre: Artmed; 2017.

164. Cuthbert B, Insel T. The Data of Diagnosis: New Approaches to Psychiatric Classification. Psychiatry. 2010 Dec;73(4):311–4.

165. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. Psychol Rev. 2001;108(3):624–52.

166. Gross JJ. Emotion Regulation: Current Status and Future Prospects. Psychol Inq. 2015 Jan 2;26(1):1–26.

167. Newman MG, Llera SJ. A novel theory of experiential avoidance in generalized anxiety disorder: A review and synthesis of research supporting a contrast avoidance model of worry. Clin Psychol Rev. 2011 Apr;31(3):371–82.

168. Paul S, Beucke JC, Kaufmann C, Mersov A, Heinzel S, Kathmann N, et al. Amygdala–prefrontal connectivity during appraisal of symptom-related stimuli in obsessive–compulsive disorder. Psychol Med. 2019 Jan;49(2):278–86.

169. Young KS, Burklund LJ, Torre JB, Saxbe D, Lieberman MD, Craske MG. Treatment for social anxiety disorder alters functional connectivity in emotion regulation neural circuitry. Psychiatry Res Neuroimaging. 2017 Mar;261:44–51.

170. Axelrod SR, Perepletchikova F, Holtzman K, Sinha R. Emotion regulation and substance use frequency in women with substance dependence and borderline personality disorder receiving dialectical behavior therapy. Am J Drug Alcohol Abuse. 2011 Jan;37(1):37–42.

171. Mennin DS, Fresco DM. What, Me Worry and Ruminate About *DSM-5* and RDoC? The Importance of Targeting Negative Self-Referential Processing. Clin Psychol Sci Pract. 2013 Sep;20(3):258–67.

172. Renna ME, Quintero JM, Soffer A, Pino M, Ader L, Fresco DM, et al. A Pilot Study of Emotion Regulation Therapy for Generalized Anxiety and Depression: Findings From a Diverse Sample of Young Adults. Behav Ther. 2018 May;49(3):403–18.

173. Brockman R, Ciarrochi J, Parker P, Kashdan T. Emotion regulation strategies in daily life: mindfulness, cognitive reappraisal and emotion suppression. Cogn Behav Ther. 2017 Mar 4;46(2):91–113.

174. Miskovic V, Keil A. Escape from harm: linking affective vision and motor responses during active avoidance. Soc Cogn Affect Neurosci. 2014 Dec;9(12):1993–2000.

175. Cisler JM, Olatunji BO, Feldner MT, Forsyth JP. Emotion Regulation and the Anxiety Disorders: An Integrative Review. J Psychopathol Behav Assess. 2010 Mar;32(1):68–82.

176. Fredrickson BL, Boulton AJ, Firestine AM, Van Cappellen P, Algoe SB, Brantley MM, et al. Positive Emotion Correlates of Meditation Practice: a Comparison of Mindfulness Meditation and Loving-Kindness Meditation. Mindfulness. 2017 Dec;8(6):1623–33.

177. Schulze L, Domes G, Krüger A, Berger C, Fleischer M, Prehn K, et al. Neuronal Correlates of Cognitive Reappraisal in Borderline Patients with Affective Instability. Biol Psychiatry. 2011;69(6):564–73.

178. Mennin DS, Fresco DM, Ritter M, Heimberg RG. An open trial of emotion regulation therapy for generalized anxiety disorder and cooccurring depression. Depress Anxiety. 2015 Aug;32(8):614–23.

179. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry. 2008 May;65(5):568–76.

180. Etkin A, Prater KE, Schatzberg AF, Menon V, Greicius MD. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry. 2009 Dec;66(12):1361–72.

181. Makovac E, Meeten F, Watson DR, Garfinkel SN, Critchley HD, Ottaviani C. Neurostructural abnormalities associated with axes of emotion dysregulation in generalized anxiety. Neuroimage Clin. 2016;10:172–81.

182. Schienle A, Ebner F, Schäfer A. Localized gray matter volume abnormalities in generalized anxiety disorder. Eur Arch Psychiatry Clin Neurosci. 2011 Jun;261(4):303–7.

183. Makovac E, Meeten F, Watson DR, Garfinkel SN, Critchley HD, Ottaviani C. Neurostructural abnormalities associated with axes of emotion dysregulation in generalized anxiety. Neuroimage Clin. 2016;10:172–81.

184. Blair K, Shaywitz J, Smith BW, Rhodes R, Geraci M, Jones M, et al. Response to emotional expressions in generalized social phobia and generalized anxiety disorder: evidence for separate disorders. Am J Psychiatry. 2008 Sep;165(9):1193–202.

185. Ball TM, Ramsawh HJ, Campbell-Sills L, Paulus MP, Stein MB. Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders. Psychol Med. 2013 Jul;43(7):1475–86.

186. Blair KS, Geraci M, Smith BW, Hollon N, DeVido J, Otero M, et al. Reduced Dorsal Anterior Cingulate Cortical Activity During Emotional Regulation and Top-Down Attentional Control in Generalized Social Phobia, Generalized Anxiety Disorder, and Comorbid Generalized Social Phobia/Generalized Anxiety Disorder. Biol Psychiatry. 2012 Sep;72(6):476–82.

187. Greenberg T, Carlson JM, Cha J, Hajcak G, Mujica-Parodi LR. Ventromedial prefrontal cortex reactivity is altered in generalized anxiety disorder during fear generalization: Research Article: Altered vmPFC Reactivity in GAD. Depress Anxiety. 2013 Mar;30(3):242–50.

188. Moon C-M, Jeong G-W. Alterations in white matter volume and its correlation with clinical characteristics in patients with generalized anxiety disorder. Neuroradiology. 2015 Nov;57(11):1127–34.

189. Cha J, Greenberg T, Carlson JM, Dedora DJ, Hajcak G, Mujica-Parodi LR. Circuit-wide structural and functional measures predict ventromedial prefrontal cortex fear generalization: implications for generalized anxiety disorder. J Neurosci. 2014 Mar 12;34(11):4043–53.

190. Gold AL, Shechner T, Farber MJ, Spiro CN, Leibenluft E, Pine DS, et al. Amygdala-Cortical Connectivity: Associations with Anxiety, Development, and Threat: 2015

ADAA Scientific Research Symposium: Anxiety, Development, and Connectivity. Depress Anxiety. 2016 Oct;33(10):917–26.

191. Wang W, Hou J, Qian S, Liu K, Li B, Li M, et al. Aberrant regional neural fluctuations and functional connectivity in generalized anxiety disorder revealed by resting-state functional magnetic resonance imaging. Neurosci Lett. 2016;624:78–84.

192. Diekhof EK, Geier K, Falkai P, Gruber O. Fear is only as deep as the mind allows. NeuroImage. 2011 Sep;58(1):275–85.

193. Cui Q, Chen Y, Tang Q, Han S, Hu S, Pang Y, et al. Disrupted dynamic local brain functional connectivity patterns in generalized anxiety disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2020 Apr;99:109833.

194. Hayes SC, Wilson KG, Gifford EV, Follette VM, Strosahl K. Experiential avoidance and behavioral disorders: A functional dimensional approach to diagnosis and treatment. J Consult Clin Psychol. 1996 Dec;64(6):1152–68.

195. Nitschke JB, Sarinopoulos I, Oathes DJ, Johnstone T, Whalen PJ, Davidson RJ, et al. Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. Am J Psychiatry. 2009 Mar;166(3):302–10.

196. Whalen PJ, Johnstone T, Somerville LH, Nitschke JB, Polis S, Alexander AL, et al. A Functional Magnetic Resonance Imaging Predictor of Treatment Response to Venlafaxine in Generalized Anxiety Disorder. Biol Psychiatry. 2008 May;63(9):858–63.

197. McClure EB, Adler A, Monk CS, Cameron J, Smith S, Nelson EE, et al. fMRI predictors of treatment outcome in pediatric anxiety disorders. Psychopharmacology. 2007 Feb 15;191(1):97–105.

198. Cameron OG, Minoshima S. Regional brain activation due to pharmacologically induced adrenergic interoceptive stimulation in humans. Psychosom Med. 2002 Dec;64(6):851–61.

199. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 2002 Aug;3(8):655–66.

200. Damsa C, Kosel M, Moussally J. Current status of brain imaging in anxiety disorders: Curr Opin Psychiatry. 2009 Jan;22(1):96–110.

201. Drevets WC. Neuroimaging Abnormalities in the Amygdala in Mood Disorders. Ann N Y Acad Sci. 2006 Jan 24;985(1):420–44.

202. LeDoux JE. Emotion Circuits in the Brain. Annu Rev Neurosci. 2000 Mar;23(1):155–84.

203. Anderson ER, Hope DA. The relationship among social phobia, objective and perceived physiological reactivity, and anxiety sensitivity in an adolescent population. J Anxiety Disord. 2009 Jan;23(1):18–26.

204. Hoehn-Saric R, Schlund MW, Wong SHY. Effects of citalopram on worry and brain activation in patients with generalized anxiety disorder. Psychiatry Research: Neuroimaging. 2004 May;131(1):11–21.

205. Godemann F, Butter C, Lampe F, Linden M, Schlegl M, Schultheiss H-P, et al. Panic disorders and agoraphobia: side effects of treatment with an implantable cardioverter/defibrillator. Clin Cardiol. 2004 Jun;27(6):321–6.

206. Beauchaine T. Vagal tone, development, and Gray's motivational theory: toward an integrated model of autonomic nervous system functioning in psychopathology. Dev Psychopathol. 2001;13(2):183–214.

207. Friedman BH. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biol Psychol. 2007 Feb;74(2):185–99.

208. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000 Dec;61(3):201–16

209. Porges, Stephen W., 2007. The polyvagal perspective. Biol. Psychol. 2007;74(2): 116–143. https://doi: 10.1016/j.biopsycho.2006.06.009.

210. Beauchaine, Theodore P, Thayer, Julian F. Heart rate variability as a transdiagnostic biomarker of psychopathology. Int. J. Psychophysiol. 2015;98(2): 338–350. https://doi: 10.1016/j.ijpsycho.2015.08.004..

211. Hofmann SG, Moscovitch DA, Litz BT, Kim H-J, Davis LL, Pizzagalli DA. The worried mind: autonomic and prefrontal activation during worrying. Emotion. 2005 Dec;5(4):464–75.

212. Everson-Rose SA, Lewis TT. PSYCHOSOCIAL FACTORS AND CARDIOVASCULAR DISEASES. Annu Rev Public Health. 2005 Apr 21;26(1):469–500.

213. Kalk N, Nutt D, Lingford-Hughes A. The role of central noradrenergic dysregulation in anxiety disorders: evidence from clinical studies. J Psychopharmacol. 2011 Jan;25(1):3–16.

214. Chalmers JA, Quintana DS, Abbott MJ-A, Kemp AH. Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. Front Psychiatry [Internet]. 11 de julho de 2014 [cited 2020 Nov 8];5. Available from: http://journal.frontiersin.org/article/10.3389/fpsyt.2014.00080/abstract

215. Kim K, Lee S, Kim J-H. Diminished autonomic neurocardiac function in patients with generalized anxiety disorder. NDT. 2016 Dec;Volume 12:3111–8.

216. Hu MX, Milaneschi Y, Lamers F, Nolte IM, Snieder H, Dolan CV, et al. The association of depression and anxiety with cardiac autonomic activity: The role of confounding effects of antidepressants. Depress Anxiety. 2019 Dec;36(12):1163–72.

217. Kubzansky LD, Kawachi I. Going to the heart of the matter. J Psychosom Res. 2000 Apr;48(4–5):323–37.

218. Murata K, Yano E, Shinozaki T. Impact of shift work on cardiovascular functions in a 10-year follow-up study. Scand J Work Environ Health. 1999 Jun;25(3):272–7.

219. Keil A, Bradley MM, Hauk O, Rockstroh B, Elbert T, Lang PJ. Large-scale neural correlates of affective picture processing. Psychophysiology. 2002 Sep;39(5):641–9.

220. Fishback GM, Chriki L, Thayer JF, Vasey MW. Heart Rate Variability Moderates the Association Between Beliefs About Worry and Generalized Anxiety Disorder Symptoms. Front Neurosci. 2020;14:569359.

221. Foa EB, Kozak MJ. Emotional processing of fear: exposure to corrective information. Psychol Bull. 1986 Jan;99(1):20–35.

222. Foa EB, Huppert, JD, Cahill, SP. Emotional processing theory: an update. In: Pathological anxiety: emotional processing in etiology and treatment. New York: Guilford Press; 2006.

223. Borkovec TD, Roemer L. Perceived functions of worry among generalized anxiety disorder subjects: Distraction from more emotionally distressing topics? J Behav Ther Exp Psychiatry. 1995 Mar;26(1):25–30.

224. Wells A. The Metacognitive Model of Worry and Generalised Anxiety Disorder. In: Davey GCL, Wells A, organizadores. Worry and its Psychological Disorders [Internet]. Chichester, UK: John Wiley & Sons Ltd; 2006 [cited 2020 Nov 11]. p. 177–99. Available from: http://doi.wiley.com/10.1002/9780470713143.ch11

225. Turk CL, Heimberg RG, Luterek JA, Mennin DS, Fresco DM. Emotion Dysregulation in Generalized Anxiety Disorder: A Comparison with Social Anxiety Disorder. Cogn Ther Res. 2005 Feb;29(1):89–106.

226. Roemer L, Orsillo SM. Expanding Our Conceptualization of and Treatment for Generalized Anxiety Disorder: Integrating Mindfulness/Acceptance-Based Approaches With Existing Cognitive-Behavioral Models. Clin Psychol (New York). 2006 May 11;9(1):54–68.

227. Bandelow B, Reitt M, Röver C, Michaelis S, Görlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol. 2015 Jul;30(4):183–92.

228. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014 May;28(5):403–39.

229. Stein MB, Sareen J. Clinical practice. Generalized Anxiety Disorder. N Engl J Med. 2015 Nov 19;373(21):2059–68.

230. Chen T-R, Huang H-C, Hsu J-H, Ouyang W-C, Lin K-C. Pharmacological and psychological interventions for generalized anxiety disorder in adults: A network meta-analysis. J Psychiatr Res. 2019 Nov;118:73–83.

231. Gonçalves DC, Byrne GJ. Interventions for generalized anxiety disorder in older adults: systematic review and meta-analysis. J Anxiety Disord. 2012 Jan;26(1):1–11.

232. Cuijpers P, Cristea IA, Weitz E, Gentili C, Berking M. The effects of cognitive and behavioural therapies for anxiety disorders on depression: a meta-analysis. Psychol Med. 2016 Dec;46(16):3451–62.

233. Hans E, Hiller W. A meta-analysis of nonrandomized effectiveness studies on outpatient cognitive behavioral therapy for adult anxiety disorders. Clin Psychol Rev. 2013 Dec;33(8):954–64.

234. Leahy R.L. Técnicas de terapia cognitiva: manual do terapeuta. 2. ed. Porto Alegre: Artmed; 2019. 516 p.

235. Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JAJ, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials. Depress Anxiety. 2018 Jun;35(6):502–14.

236. Kabat-Zinn J. Mindfulness. Mindfulness. 2015 Dec;6(6):1481–3.

237. Gu J, Strauss C, Bond R, Cavanagh K. How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. Clin Psychol Rev. 2015 Apr;37:1–12.

238. Shi W, He X, Han X, Wang N, Zhang N, Wang X. The interventional effects of loving-kindness meditation on positive emotions and interpersonal interactions. NDT. 2015 May;1273.

239. Hölzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, et al. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res. 2011;191:36–43.

240. Jang JH, Jung WH, Kang DH, Byun MS, Kwon SJ, Choi CH, et al. 2011. Increased default mode network connectivity associated with meditation. Neurosci. Lett. 2011;487:358–362..

241. Lin Y, Fisher ME, Roberts SMM, Moser JS. Deconstructing the Emotion Regulatory Properties of Mindfulness: An Electrophysiological Investigation. Front Hum Neurosci [Internet]. 2016 Sep 7 [cited 2020 Nov 7];10. Available from: http://journal.frontiersin.org/Article/10.3389/fnhum.2016.00451/abstract

242. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage. 2004 Oct;23(2):483–99.

243. Lazar SW, Kerr CE, Wasserman RH, Gray JR, Greve DN, Treadway MT, et al. Meditation experience is associated with increased cortical thickness. Neuroreport. 2005;16:1893–1897.

244. Pavlov SV, Reva NV, Loktev KV, Korenyok VV, Aftanas LI. Impact of long-term meditation practice on cardiovascular reactivity during perception and reappraisal of affective images. Int J Psychophysiol. 2015 Mar;95(3):363–71.

245. Hoge EA, Bui E, Marques L, Metcalf CA, Morris LK, Robinaugh DJ, et al. Randomized Controlled Trial of Mindfulness Meditation for Generalized Anxiety Disorder: Effects on Anxiety and Stress Reactivity. J Clin Psychiatry. 2013 Aug 15;74(08):786–92.

246. Pender NJ, Murdaugh CL, Parsons MA. Health promotion in nursing practice. 5. ed. Upper Saddle River, NJ: Pearson/Prentice Hall; 2006.

247. Cockerham WC. Health lifestyle theory and the convergence of agency and structure. J Health Soc Behav. 2005;46: 51–67.

248. Posadzki P, Musonda P, Debska G, Polczyk R. Psychosocial conditions of quality of life among undergraduate students: a cross sectional survey. Appl Res Qual Life. 2009;4:239–258

249. Maher JP, Doerksen SE, Elavsky S, Conroy DE. Daily satisfaction with life is regulated by both physical activity and sedentary behavior. *J Sport Exerc Psychol.* 2014;36(2):166–178. doi: 10.1123/jsep.2013-0185.

250. Blacklock RE., Rhodes RE., Brown SG. Relationship between regular walking, physical activity, and health-related quality of life. *J Phys Act Health.* 2007;4(2):138–152. doi: 10.1123/jpah.4.2.138.

251. Santos L de M dos, Da Ros MA, Crepaldi MA, Ramos LR. Grupos de promoção à saúde no desenvolvimento da autonomia, condições de vida e saúde. Rev Saúde Pública. 2006 Apr;40(2):346–52.

252. Bhattacharjee D, Rai A, Singh N, Kumar P, Munda S, Das B. Psychoeducation: A Measure to Strengthen Psychiatric Treatment. Ind Psychiatry J. 2011 Apr 1;14:33–9.

253. Lemes CB, Neto JO. Aplicações da psicoeducação no contexto da saúde. Temas Psicol. 2017;25(1):17–28.

254. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.

255. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50–5.

256. Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). Depress Anxiety. 2001;13(4):166–78.

257. DeSousa DA, Moreno AL, Gauer G, Manfro GG, Koller SH. Revisão sistemática de instrumentos para avaliação de ansiedade na população brasileira. Avali Psicol. 2013;12(3):13.

258. Galluci Neto J GN J, Campus Junior MS, Hubner CK. Escala de Depressão de Hamilton (HAM-D): revisão dos 40 anos de sua utilização. 2001;3(1):6.

259. Carneiro AM, Fernandes F, Moreno RA. Hamilton depression rating scale and montgomery–asberg depression rating scale in depressed and bipolar I patients: psychometric properties in a Brazilian sample. Health Qual Life Outcomes. 2015 Dec;13(1):42.

260. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida "WHOQOL-bref". Rev Saúde Pública. 2000 Apr;34(2):178–83.

261. Cancian ACM, Souza LAS de, Silva VHP e, Machado W de L, Oliveira M da S. Psychometric properties of the Brazilian version of the Difficulties in Emotion Regulation Scale (DERS). Trends Psychiatry Psychother. 2019 Mar;41(1):18–26.

262. Beck JG, Stanley M, Zebb B. Psychometric properties of the Penn State Worry Questionnaire in older adults. Journal of Clinical Geropsychology. 1995 Jan 1;1:33–42.

263. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the penn state worry questionnaire. Behav Res Ther. 1990;28(6):487–95.

264. Castillo C, Macrini L, Cheniaux E, Landeira-Fernandez J. Psychometric properties and latent structure of the Portuguese version of the Penn State Worry Questionnaire. Span J Psychol. 2010 May;13(1):431–43.

265. Lang PJ, Bradley MM, Cuthbert. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Technical Report A-6. Gainesville, FL: University of Florida; 2005.

266. Senior C, Russell T, Gazzaniga MM. Methods in mind. London: MIT Press; 2009.

APÊNDICE A – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nº do projeto GPPG 160301

Título do Projeto: "Ensaio Clínico Randomizado Comparando Tratamento Baseado em Mindfulness versus Tratamento Farmacológico versus Grupo Qualidade de Vida em Pacientes com Transtorno de Ansiedade Generalizada. "

Você está sendo convidado a participar de uma pesquisa cujo objetivo é comparar três diferentes tratamentos para o Transtorno de Ansiedade Generalizada, bem como avaliar os mecanismos de possível melhora, sendo eles o (1) Tratamento Medicamentoso (farmacológico) com Fluoxetina*;* (2) Prática de *Mindfulness* e; (3) Participação em Grupo de Qualidade de Vida. Esta pesquisa está sendo realizada pelo Serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre (HCPA). O Transtorno de Ansiedade Generalizada é um transtorno caracterizado por sintomas físicos e emocionais, que tem um curso crônico e que traz grande prejuízo físico e emocional para os seus portadores. A Fluoxetina é, atualmente, um dos tratamentos de escolha para o Transtorno de Ansiedade Generalizada, sendo o tratamento padrão indicado. O *Mindfulness* é uma prática ligada ao budismo que lembra a meditação, seu papel em promover a saúde tem sido estudado, possuindo benefício no tratamento de ansiedade. Sabemos também que alterações de hábitos de qualidade de vida são fundamentais no controle da ansiedade. Porém, como não há estudos que comparem esses possíveis tratamentos, este é o objetivo desta pesquisa.

Se você aceitar participar da pesquisa, os procedimentos envolvidos em sua participação são os seguintes:

Você será sorteado para um dos grupos abaixo (o grupo não pode ser escolhido pelo participante):

1. Grupo Medicamento: receberá indicação de utilizar Fluoxetina e terá acompanhamento psiquiátrico, em forma de consulta individual com duração aproximada de 20 minutos, uma vez por semana por 8 semanas.
2. Grupo *Mindfulness*: encontros semanais (uma vez por semana) com duração de duas horas, realizados em grupo, com orientação sobre a prática de *Mindfulness*, realizada por um psicólogo durante 8 semanas.
3. Grupo Qualidade de Vida: encontros semanais (uma vez por semana) com duração de duas horas, realizados em grupo, com orientações sobre qualidade de vida, realizado por uma psicóloga durante 8 semanas.

Além de realizar o tratamento acima, você fará as seguintes avaliações:

- Avaliação diagnóstica psiquiátrica e preenchimento de alguns questionários sobre suas emoções com duração média de 1 hora e 30 minutos no primeiro encontro;
- Novo preenchimento de questionários sobre suas emoções com duração aproximada de 30 minutos. Você responderá estes questionários na semana 5 e semana 8 do estudo, bem como 12 semanas após o término do estudo;
- Contato telefônico: ainda, na semana 24 após o término do tratamento, faremos breve avaliação de como você está emocionalmente por contato telefônico.

Você poderá ser sorteado para realizar os seguintes exames:

- Extração de DNA e coleta de sangue: serão feitas uma coleta de saliva e uma coleta de sangue (5 ml - equivalente a uma colher de chá) para que possamos avaliar marcadores inflamatórios e genéticos que possam ter alguma associação com o Transtorno de Ansiedade

Generalizada. As coletas são realizadas antes e após o tratamento. Sua duração é de aproximadamente 30 minutos.

- Avaliação da variabilidade da frequência cardíaca e do *Error Related Negativity* (eletroencefalograma): esses são exames não invasivos que visam avaliar como está o seu ritmo cardíaco e de sua atividade elétrica cerebral. Essas medições são realizadas através do contato do aparelho superficialmente com a pele. Os exames serão realizados antes e após o tratamento. Sua duração é de aproximadamente 30 minutos.

- Avaliação com neuroimagem funcional: um exame em uma máquina de ressonância magnética funcional onde você ficará por aproximadamente 40 minutos e realizará algumas tarefas simples dentro dela. Este exame será realizado antes e após o tratamento.

Os riscos associados ao uso de Fluoxetina são náuseas, dor de cabeça, diminuição do apetite, dor abdominal, diarreia, alteração do sono, tremor, ansiedade e nervosismo que costumam durar de duas a três semanas após o início do tratamento. Distúrbio da coagulação, alteração do sódio sérico e reações alérgicas são eventos possíveis, de maior gravidade, mas raros. Os possíveis desconfortos da participação no grupo *Mindfulness* são decorrentes da conscientização do seu jeito de funcionar emocionalmente e algum nível de tensão corporal, além do possível constrangimento de compartilhar informações pessoais em grupo. Os desconfortos associados à participação no Grupo Qualidade de Vida também estão associados ao possível constrangimento de compartilhar informações pessoais em grupo.

Em relação ao preenchimento dos questionários, você pode ficar cansado ou se sentir constrangido por responder perguntas sobre os próprios sentimentos. A coleta do sangue pode trazer algum desconforto ou leve dor no momento da coleta, bem como ocasionar um hematoma (mancha roxa) no local que deverá desaparecer em alguns dias. A coleta da saliva não adiciona riscos. A realização dos exames de variabilidade da frequência cardíaca e do eletroencefalograma não oferecem riscos conhecidos, poderá haver algum desconforto relacionado à utilização dos eletrodos que realizam a medição e ficam em contato superficial com a pele. O exame de neuroimagem funcional é um exame que não oferece riscos, porém pode ser desconfortável por ser um pouco barulhento e realizado em uma máquina parecida com um tubo com um dos lados fechado, o que pode ser desconfortável.

O participante poderá se beneficiar por receber uma avaliação clínica e psicológica estruturada. Espera-se que haja uma redução dos sintomas de ansiedade e de preocupação para os participantes, assim como uma melhora na qualidade de vida desses e dos indivíduos com os quais os participantes convivem. Também, espera-se conhecer melhor os mecanismos do Transtorno de Ansiedade Generalizada, bem como os mecanismos de melhora, o que poderá ajudar outros pacientes no futuro.

Sua participação na pesquisa é totalmente voluntária, ou seja, não é obrigatória. Caso você decida não participar, ou ainda, desistir de participar e retirar seu consentimento, não haverá nenhum prejuízo ao atendimento que você recebe ou possa vir a receber na instituição.

Não está previsto nenhum tipo de pagamento pela sua participação na pesquisa e você não terá nenhum custo com respeito aos procedimentos envolvidos. Caso ocorra alguma intercorrência ou dano, resultante de sua participação na pesquisa, você receberá atendimento e o encaminhamento necessário.

Os dados coletados durante a pesquisa serão sempre tratados confidencialmente. Os resultados serão apresentados de forma conjunta, sem a identificação dos participantes, ou seja, o seu nome não aparecerá na publicação dos resultados. Após a utilização do material biológico coletado neste projeto, este material será conservado. Nenhum uso comercial do material poderá ser feito sem sua prévia autorização.

Caso você tenha dúvidas, poderá entrar em contato com o pesquisador responsável Profª Drª Gisele Gus Manfro, pelo telefone (51) 3359-8294, com o pesquisador Drª Marianna de Abreu Costa, pelo telefone (51) 3359-8943, ou com o Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre (HCPA), pelo telefone (51) 3359-7640, ou no 2º andar do HCPA, sala 2227, de segunda à sexta, das 8h às 17h.

Esse Termo é assinado em duas vias, sendo uma para o participante e outra para os pesquisadores.

_____	_____
Nome do participante da pesquisa	Nome do pesquisador que aplicou o Termo
_____	_____
Assinatura	Assinatura

Local e Data: _____

APÊNDICE B – ARTIGO PUBLICADO NO PSYCHOTHERAPY AND PSYCHOCOMATICS

Publicado na revista Psychotherapy and Psychosomatics

A Three-Arm Randomized Clinical Trial Comparing the Efficacy of a Mindfulness-Based Intervention with an Active Comparison Group and Fluoxetine Treatment for Adults with Generalized Anxiety Disorder

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Abstract

Introduction

Mindfulness-based interventions have been studied as an alternative treatment for anxiety disorders, but there are few studies comparing these with established treatments.

Objective

To evaluate the efficacy of a Body in Mind Training (BMT) program for adults with generalized anxiety disorder (GAD) compared with an active comparison group (QoL) and treatment with fluoxetine (FLX).

Methods

This study comprises a three-arm parallel-group randomized clinical trial (ClinicalTrials.gov ID: NCT03072264). Adults with a primary diagnosis of GAD and no current treatment were recruited from the community and randomized in a ratio 1:1:1. The primary outcomes were assessed through Hamilton Anxiety Rating Scale (HAM-A) and Penn State Worry Questionnaire (PSWQ) at week 8. Data were analyzed using a superiority analysis (BMT vs. QoL) and a non-inferiority analysis (BMT vs. FLX).

Results

A total of 249 participants were included and 223 were analyzed (76 BMT, 79 FLX, 68 QoL). All groups improved after intervention. However, BMT was not superior to QoL at week 8 (mean difference = -1.36; p = .47), nor was it non-inferior to FLX as assessed through HAM-A (mean difference = 3.5; CI 95% -0.06 to 7.06; non-inferiority margin = -2.43; p = .054). The QoL group (mean difference = 3.54; p = .04) and FLX (mean difference = -7.72; CI 95% -10.89 to -4.56; non-inferiority margin = -2.09; p < .001) were superior to BMT in reducing PSWQ.

Conclusion

Our data suggested that BMT should not be considered as an effective mindfulness protocol to improve GAD in its current format.

Introduction

Generalized anxiety disorder (GAD) is one of the most prevalent mental disorders affecting millions of people worldwide (1). It is characterized by persistent worry associated with social and occupational dysfunction (2,3). Despite this, only a minority of patients receive adequate treatment (4). Conversely, treatment responses from available options such as pharmacotherapy and cognitive behavioral therapy (CBT) range from 44% to 81% (5), and only 38% of GAD patients will remit in the long term (6). Furthermore, adherence to CBT is challenging and discontinuation of pharmacotherapy due to adverse side effects is common (7). Therefore, it is important to investigate and compare the efficacy of other alternative therapies for this condition with standard treatments in order to decrease the burden attributed to GAD.

Since the late 1970s, mindfulness-based interventions (MBIs) have been studied as an alternative method for treating mental disorders (8). Mindfulness-based cognitive therapy (MBCT) is already recommended by the National Institute for Health and Care Excellence in the UK as a first-line treatment for recurrent depression (9). Previous reviews have already described the efficacy of MBIs to treat anxiety symptoms in clinical samples (10–12) and a recent meta-analysis reported that MBIs are a promising therapeutic option for decreasing distress symptoms in patients with anxiety disorders such as GAD (13). However, the few studies that have assessed the efficacy of MBIs in treating patients with GAD had an open-label design (14,15), small sample sizes (14–17), mixed sample (15,17,18), or assessed MBIs as an adjunct to pharmacological treatment (17). Moreover, the two larger clinical trials evaluating the efficacy of different MBIs (Mindfulness Based Stress Reduction - MBSR or MBCT) in

GAD patients (19,20) reported conflicting results, and there are no studies comparing MBIs to established pharmacological treatments for GAD.

However, since the use of established protocols such as MBCT and MBSR to treat GAD showed conflicting results, this present study aimed to assess the efficacy of a new mindfulness-based protocol, the Body in Mind Training (BMT) program, in comparison with an active control condition named Quality of Life-Psychoeducation Group (Qol) and with a first-line pharmacological treatment (fluoxetine, FLX) in reducing anxiety symptoms in patients with a GAD diagnosis. We chose BMT because its protocol is designed and effective for treating more severe mental illness (21). BMT is enhanced by body movement, which is intended to improve attention anchoring and can be helpful for patients with severe anxiety (21,22). We hypothesize that the mindfulness group would be superior to the active comparison group in reducing anxiety symptoms and not inferior to FLX treatment.

Materials and Methods

Design

This study is a single-blinded parallel three-arm randomized clinical trial. Patients were evaluated prior to randomization (baseline), at week 5, and at the end of treatment (week 8). The trial was registered at ClinicalTrials.gov (NCT03072264) and all participants gave their written informed consent before entering the study (Ethics Committee of Hospital de Clínicas de Porto Alegre, number 20160301).

Participants

We recruited the participants from the community through media advertisement, inviting individuals with GAD symptoms to participate in this study. Patients were screened by phone call with a brief measure for assessing GAD (Generalized Anxiety Disorder 7-item [GAD-7] scale) and we scheduled a diagnostic evaluation interview with trained clinicians (psychologists or psychiatrists) for those who were potentially eligible: (a) a score of 10 or higher on the GAD-7 scale (23); (b) aged 18 years or older; (c) not currently in treatment with CBT or medication for anxiety; (d) no history of failing a trial with FLX; (e) no diagnosis of bipolar, psychotic, or substance use disorder (other than tobacco); (f) no current pregnancy or breastfeeding.

After the clinical evaluation, we included participants provided they were: (a) adult; (b) had a primary GAD diagnosis as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) adapted to reflect the DSM-5 criteria; (c) available to attend the sessions; and (d) not

currently in treatment (psychopharmacological or psychotherapeutic) for anxiety symptoms. Exclusion criteria were: (a) comorbidities that required treatment, such as lifetime bipolar disorder, lifetime psychotic disorder, current eating disorder, current antisocial personality disorder, substance use disorder (other than tobacco), in the last six months and suicidal ideation in the last six months as assessed by the M.I.N.I.; (b) Hamilton Depression Rating Scale (HAM-D) score ≥23; (c) contraindication to the use of FLX (e.g., use of thioridazine, monoamine oxidase inhibitors, or some antiretroviral drugs, had coagulopathy or were taking an anticoagulant), or to undergo mindfulness-based intervention (e.g., clinical instability or immobility); and (d) pregnancy, breastfeeding, or the wish to become pregnant during the study. Data collection and interventions were performed at the Hospital de Clínicas de Porto Alegre (HCPA) in the south of Brazil.

Treatment conditions

Experimental Group: Body in Mind Training (BMT)

A qualified BMT psychologist with eight years' experience (TT) conducted the BMT protocol in weekly 2-hour sessions for eight weeks. Each treatment group consisted of 8 to 15 participants. The BMT protocol comprises five 2-hour sessions and has already been assessed in adult participants with severe and enduring mental health conditions, psychotic inpatients (24), healthy individuals (such as health-care staff), and patients with bipolar disorder (21,22,25). It combines concepts from the neurosciences, mindfulness, embodied cognition, psychology, and tai chi, and gently and non-judgmentally uses the body as an anchor to attention and proprioceptive processes (21,22). In this study, we added three final sessions on self-compassion exercises to the original protocol. For more details on the protocol description, see the *Supplemental Material*. As homework, the participants were encouraged to engage in 20 minutes' practice each day. The sessions were delivered as detailed in the BMT protocol and protocol adherence was assured through direct weekly supervision by the therapist who first developed this BMT protocol. Participants randomized to the BMT group were not allowed to take any psychiatric medication during the trial.

Quality of Life and Psychoeducation Group (QoL)

We used the QoL group as an active comparison to the BMT group. It comprised 2-hour weekly sessions for eight weeks based on psychoeducational principles (26), like empathy and therapeutic alliance, delivered by a trained psychologist (FG). Each treatment group consisted of 8 to 15 participants. In the first five sessions, the psychologist introduced and discussed

important aspects for controlling anxiety in a class format followed by a group discussion on the following topics: GAD psychoeducation; substance use; sleep hygiene; physical activity; and healthy eating. At the end of each meeting, the therapist suggested that participants should engage in the learned healthier habits and they should discuss the difficulties they encountered in implementing these new habits during the final three sessions. For more detail on the QoL group description and procedure see the *Supplemental Material*. We decided to use a psychoeducation - quality of life active control group in order to compare BMT intervention with placebo and common unspecific factors of psychotherapeutic group interventions as well as with evidence-based interventions used to manage anxiety (27,28). Participants randomized to the QoL group were not allowed to take any medication for psychiatric symptoms during the trial.

Fluoxetine Treatment (FLX)

An experienced clinical psychiatrist assessed the participants individually. Patients had to come to the appointment every three weeks but could come every week if they wanted to see the psychiatrist. Patients could contact the psychiatrist for any doubts about medication using the phone chat group. Treatment was given for eight weeks with FLX from 20 to 60 mg/day. The initial dose was 20 mg. After week 3, the clinician could increase the dose up to 40 mg for all individuals with a HAM-A score >10 and to 60 mg if they still scored HAM-A >10 in week 6. The dose titration was also based on patients' tolerability and acceptance. The psychiatrist informed the participants about medication effects and side effects but was not allowed to give GAD psychoeducation during the appointments. The adherence of participants to FLX treatment was assessed by the control of blister packs. We used FLX since the recent literature and meta-analyses do not demonstrate that it has better efficacy than a specific selective serotonin reuptake inhibitor antidepressant (SSRI) to treat GAD (29,30). Furthermore, FLX is well tolerated and available free of charge through all public services in Brazil.

Assessments

All participants were evaluated using the M.I.N.I., GAD-7, and HAM-D to assess eligibility. Clinician evaluators blinded to the treatment conditions assessed participants through the Hamilton Anxiety Rating Scale (HAM-A) and the Clinical Global Impressions Scale-Severity (CGI-S) and -Improvement (CGI-I) at baseline, week 5 and at the end of the trial (week 8). Participants also answered the WHOQOL-Bref and the Penn State Worry Questionnaire (PSWQ) at baseline, weeks 5 and 8, and the GAD-7 scale at the end of the

intervention. GAD-7 was not registered as a secondary outcome at ClinicalTrials.gov. At the end of the study, all participants received psychoeducation and psychiatric orientation. We also referred all participants who needed further assistance to the public health system, either to start or to maintain treatment.

Diagnostic assessment

The M.I.N.I. is a structured validated clinical diagnostic interview to assess psychiatric diagnoses based on DSM-IV and CID-10 (31). It was adapted and validated for use in the Brazilian population (32). In this study, we adapted the GAD questions to DSM-5 criteria adding the observation that at least some symptoms associated with worry and anxiety *"have to be present for more days than not for the past 6 months"* (33).

Primary outcomes

Clinician-rated – Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a well-validated rating scale designed to evaluate the severity of anxiety symptoms (34). This scale comprises 14 items, all rating from zero (no symptom) to 4 (the worst severity symptom). A total score between 14 and 17 indicates mild anxiety. A score ranging from 18 to 24 indicates moderate anxiety, and from 25 to 30 characterizes moderate to severe anxiety (34). The total score ranges from 0 to 56. The inter-rater reliability for HAM-A ratings was high (kappa = 0.968; CI 95% 0.854 to 0.996).

Patient-rated – Penn State Worry Questionnaire (PSWQ)

PSWQ is a self-report rating scale developed to measure worry with an excellent internal consistency and good test–retest reliability (35). It comprises 16 items with scores ranging from 1 to 5, with good ability to discriminate GAD in individuals (35). It is validated for the Brazilian population(36) and the total score ranges from 16 to 80.

Secondary outcomes

Clinician-rated – Clinical Global Impressions Scale (CGI)

CGI is an instrument developed to help clinicians assess severity (CGI-S) and improvement (CGI-I) of psychopathology (37). CGI-S rating scores vary from 1 (normal—not at all ill) to 7 (among the most extremely ill patients), and CGI-I from 1 (very much improved) to 7 (very much worse).

Patient-rated – Generalized Anxiety Disorder 7-item (GAD-7) Scale

The GAD-7 screening scale is a validated brief Likert-type self-report scale with seven items, which can also be used to evaluate GAD severity (23). This instrument has already been validated for the Brazilian population (38) and the total score ranges from 0 to 21.

Clinician-rated – Hamilton Rating Scale for Depression (HAM-D)

The HAM-D is an instrument developed to assess depressive symptoms (39,40). It contains 17 items, and each item score ranges from zero (no symptom) to 4 (the worst symptom severity). This scale has already been validated for Brazilian-Portuguese (41) and the total score ranges from 0 to 52.

Patient-rated – WHOQOL-Bref (WHOQOL)

The WHOQOL-Bref is a self-report scale with 26 items that measure quality of life. It comprises two general items and 24 items representing four different quality-of-life domains: physical, psychological, social relations, and the environment. It is validated for the Brazilian-Portuguese population (42) and the total score ranges from 0 to 100.

Randomization and masking

Participants were randomly allocated in a ratio 1:1:1 to receive one of the three interventions: BMT, QoL, or FLX. The randomization was performed using sealed and opaque envelopes. The patients themselves took an envelope from a box with the intervention they were selected to participate in after baseline evaluation. Twenty-one participants per intervention were recruited in each wave and there was an equal chance in each wave to be allocated to any of the three interventions.

Blinded evaluators performed the evaluation assessments at week 5 and at the end of the intervention (week 8). Because of the nature of the interventions, neither therapists nor participants could be masked. However, participants were unaware of the experimental/control groups. Also, they were instructed not to inform the blinded evaluators about which intervention they were receiving.

Primary and secondary outcomes

The primary outcome (adjusted for potential confounders) is the clinical efficacy of treatment assessed by the HAM-A (clinician-rated) and PSWQ (patient-rated) at the end of the treatment (week 8). We chose to use HAM-A as primary outcome because it is the most used

rating scale to evaluate GAD patients. We used PSWQ as the other main outcome because it assesses worry, the core symptom of GAD. Secondary outcome measures included the evaluation of GAD-7, WHOQOL, and rates of response and remission. All outcome measures were evaluated at baseline, week 5, and at the end of treatment (week 8), except for the GAD-7, which was assessed only at baseline and at the end of treatment. Response was defined as at least 50% reduction in HAM-A total score at week 8 compared with baseline (43). Remission was defined as a HAM-A total score equal to or less than 7 at week 8 (43).

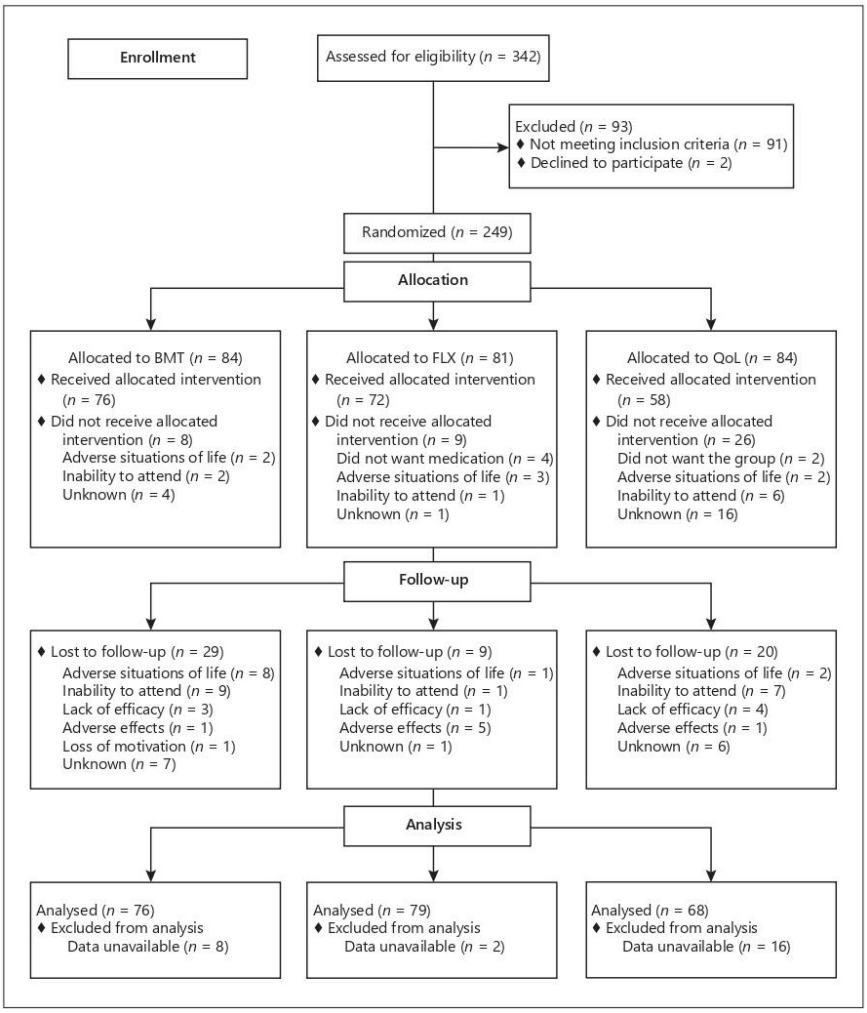

Figure 1: CONSORT Flow Diagram

Statistical analysis

Subjects were included in the analysis if they attended the first session. We analyzed the data using the generalized estimating equation (GEE) for both primary and secondary outcomes adjusted for gender, age, education level, major depression, agoraphobia, and HAM-D scores according to intention-to-treat analyses. We considered the rating scale score at baseline to

investigate time, group, and time-by-group interactions. All analyses considered two within-subject levels (time and therapy group) in order to adjust for clustering effects. Moreover, we analyzed data using the GEE for both primary and secondary outcomes as registered on ClinicalTrials.gov, i.e., without adjustment for nominal and statistically significant differences between groups (referred to in the text as unadjusted analysis). The difference between groups over time was provided by the time-by-group Wald X^2 test from GEE analysis and we used data from week 8 to report the mean differences. Missing data was handled using full information maximum likelihood (FIML). Our main hypothesis was tested using two sets of comparisons: a superiority analysis comparing BMT with QoL (placebo) and a non-inferiority analysis comparing BMT with FLX (active treatment). Moreover, we used Cohen's *d* test for paired samples to calculate the effect size considering the comparison between FLX and QoL groups and BMT (BMT minus controls).

Considering the power of 80% and a significance level of 5%, a sample of 64 patients per group (total of 192) was calculated to detect an effect size difference of 0.5 for HAM-A between BMT and QoL. We chose the effect size of 0.5 in accordance with previous studies that considered it clinically relevant (44). The non-inferiority margin was based on the point estimate of 50% of the difference in each outcome score in the comparison of Qol (placebo) with FLX (active) (45). This approach was chosen because we hypothesized that BMT would be at least 50% as effective as FLX. Non-inferiority could be claimed if the lower boundary of the confidence interval around the mean difference between the scores in the BMT group versus the FLX group exceeded this value. A two-sided *p* value of .05 or less was considered to be statistically significant. We conducted all analyses using the IBM SPSS Statistics, Version 25.0 program (IBM Corp. Released 2017).

Ethical statement

The ethical review board of *Hospital de Clínicas de Porto Alegre* approved the study (number 20160301) and all participants signed written informed consent prior to inclusion.

Deviations from the registered protocol (NCT03072264)

The primary analysis registered in the clinical trials did not describe that we were going to adjust our data for gender, age, education level, major depression, agoraphobia, and HAM-D score. We had to perform these adjustments because of the between-group differences in these variables observed at the baseline evaluation. However, results from the unadjusted analysis were largely similar to the adjusted analysis, with two exceptions. The unadjusted

analysis showed lack of superiority of the QoL group compared with BMT for reducing worry symptoms using the PSWQ (mean difference = -1.91; p = .401), and no significant time-by-group interaction for quality of life scores using the WHOQOL scale (p = .16). Additional measures registered as secondary outcomes will be reported elsewhere and are used merely as measures of possible mechanisms associated with the described interventions.

Results

Baseline

Patients were recruited and included from January 2017 to August 2018 in four waves (approximately one wave of around 60 participants each semester). The first wave of participants started treatment in March 2017 and the last wave ended treatment in December 2018. A total of 342 individuals were selected to undergo clinical evaluation after the first phone call screening interview, which assessed 1109 individuals. After the clinical interview, we included 249 participants. Of those, 84 were randomized to BMT, 81 to FLX, and 84 to QoL. The time for recruiting participants varied from six to eight weeks and all three interventions started at the same time in each wave (including in the FLX group). See *Figure 1* for a CONSORT flow chart of the sample selection and the final sample that was included in the analyses.

The baseline sample comprised mainly female patients (79.5%; n = 198) and the mean age was 35.28 (±12.47) years old. The majority of the participants had a good level of education (completed high school at least), and the main comorbidities were major depression, panic disorder, agoraphobia, and social anxiety disorder. A small number of participants (less than 3% in all groups) were doing meditation or yoga (from experimental classes to two years of practice) at the time of enrollment or had done these activities in the past (16.5%). There was no difference between participants from the interventions groups in relation to current (3/84 [3.6%] in BMT, 2/81 [2.5%] in FLX, and 2/84 [2.4%] in QoL; chi-squared test = 0.623) or past meditation or yoga practices (12/84 [14.3%] in BMT, 15/81 [18.5%] in FLX, and 14/84 [16.6%] in QoL; chi-squared test = 0.65). No participants had prior experience of any mindfulness protocol. For more details about baseline sample characteristics of randomized patients see Table 1.

Table 1. Baseline characteristics of randomized patients

	BMT group (n = 84)	FLX group (n = 81)	QoL group (n = 84)	p value[a]
Mean age, years (SD)	36.61 (14.2)	35.21 (11.7)	34 (11.2)	0.405
Female sex	62 (73.8)	68 (84)	68 (81)	0.251
Level of education				0.445
Incomplete elementary school	4 (4.8)	0	0	
Completed elementary school	0	1 (1.2)	0	
Incomplete high school	1 (1.2)	2 (2.5)	3 (3.5)	
Completed high school	21 (25)	23 (28.4)	20 (24.4)	
Incomplete higher education	29 (34.5)	24 (29.6)	31 (37.8)	
Completed higher education	20 (23.8)	17 (21.0)	16 (19.5)	
Postgraduate/graduate	8 (9.5)	14 (17.3)	13 (15.9)	
Axis I diagnosis				
Major depression	32 (38.1)	22 (27.2)	35 (41.7)	0.13
Panic disorder	14 (16.7)	8 (9.9)	14 (16.7)	0.361
Agoraphobia	10 (11.9)	5 (6.2)	17 (20.2)	**0.025**
Obsessive-compulsive disorder	6 (7.1)	2 (2.5)	5 (6)	0.449
Social anxiety	13 (15.5)	7 (8.6)	14 (16.7)	0.271
Posttraumatic stress disorder	5 (6)	6 (7.4)	1 (1.2)	0.121
Mean HAM-D score (SD)	12.69 (4.3)	15.11 (5.3)	15.02 (5.1)	**0.002**
Mean GAD-7 score (SD)	15.55 (3.1)	15.95 (2.8)	15.42 (3.1)	0.507
Mean HAM-A score (SD)	27.53 (8.9)	29.25 (8.6)	28.16 (7.6)	0.433
Mean CGI-S score (SD)	4.42 (0.9)	4.32 (0.7)	4.53 (0.7)	0.266
Mean PSWQ score (SD)	61.85 (7.1)	62.41 (7.6)	60.58 (8.4)	0.405
Mean WHOQOL-BREF score (SD)	61.85 (7.2)	62.42 (7.6)	60.58 (8.4)	0.367

Values express n (%), unless otherwise indicated. Bold type denotes $p < 0.05$ BMT, Body in Mind Training; CGI-S, Clinical Global Impressions Scale – Severity; FLX, fluoxetine; GAD-7, Generalized Anxiety Disorder 7-item scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Rating Scale for Depression; PSWQ, Penn State Worry Questionnaire; QoL, Quality of Life and Psychoeducation; WHOQOL-BREF, WHO Quality of Life Scale.

[a] Estimated by χ^2 test or Fisher's exact test for categorical variables, and ANOVA for continuous variables with normal distributions or the nonparametric test for independent samples to continuous variables with no normal distribution.

Attrition

Of the participants who attended the first session, 61.8% completed BMT, 87.5% completed FLX, and 65.5% completed the QoL group intervention. We could observe differences in attrition rate among study conditions (Pearson's chi-squared = 17.028; df = 4; p = .02). Residual analysis revealed that the FLX group had more completers compared with the BMT or QoL groups, but there were no differences between these last two groups. In addition to attrition analysis, we also assessed the deterioration rate throughout HAM-A scores as recommended by Guidi *et al.*'s guidelines (29). Twenty-four participants had worse scores at the end of the intervention compared with baseline scores: 13 in BMT (28.2%), 4 in FLX (6.6%), and 7 in the QoL group (18.4%). The Pearson's chi-squared test showed a significant difference between rates (9.191; df = 2; p = .01). Residual analysis revealed that participants in the FLX group deteriorated less compared with the other groups; however, there was no difference between BMT and QoL groups.

Table 2. Model parameters from the Generalized Estimating Equation

	Estimated means[a]			Significance testing[a]			Adjusted mean differences in week 8 (95% CI) *p* value[a]		Noninferiority assessment	
	BMT mean (SE) [a]	QoL mean (SE) [a]	FLX mean (SE) [a]	time Wald χ^2 (*p*)	group Wald χ^2 (*p*)	time × group Wald χ^2 (*p*)	BMT vs. QoL	FLX vs. BMT	FLX vs. QoL	margin (50% FLX)
HAM-A				164.238	3.591	**15.453**	−1.36	−3.5	−4.86	−2.43
Baseline	29.91 (0.8)	29.69 (0.8)	30.70 (0.7)	**(<0.001)**	(0.166)	**(0.004)**	(−5.05 to	(−7.06 to 0.06)	(−8.4 to −1.32)	
Week 5	24.27 (1.3)	20.38 (1.3)	21.06 (1.4)				2.33)	*p* = 0.054	***p* = 0.007**	
Week 8	21.10 (1.4)	22.46 (1.5)	17.60 (1.4)				*p* = 0.47			
GAD-7				87.839	3.377	**10.837**	−0.35	−2.9	−3.25	−1.63
Baseline	15.15 (0.8)	16.59 (0.5)	17.01 (0.5)	**(<0.001)**	(0.185)	**(0.004)**	(−3.54 to	(−5.27 to −0.52)	(−6.03 to	
Week 5	–	–	–				2.84)	***p* = 0.017**	−0.47)	
Week 8	9.74 (1.1)	10.09 (1.3)	6.85 (0.6)				*p* = 0.83		***p* = 0.022**	
PSWQ				600.765	8.566	**57.835**	3.54	−7.72	−4.18	−2.09
Baseline	57.90 (0.9)	60.84 (0.9)	62.92 (0.9)	**(<0.001)**	**(0.014)**	**(<0.001)**	(0.16 to 6.92)	(−10.89 to	(−7.53 to	
Week 5	58.88 (1.3)	56.26 (1.5)	52.35 (1.3)				***p* = 0.04**	−4.56)	−0.84)	
Week 8	48.43 (1.2)	44.89 (1.5)	40.71 (1.3)					***p* < 0.001**	***p* = 0.014**	
WHOQOL-BREF				79.405	2.353	**12.840**	2.94	5.89	8.83	4.42
Baseline	45.76 (1.2)	45.96 (1.7)	45.99 (1.4)	**(<0.001)**	(0.308)	**(0.012)**	(−3.49 to	(−0.45 to 12.22)	(2.45 to 15.22)	
Week 5	57.76 (2.3)	60.46 (2.1)	59.47 (2.3)				9.38)	*p* = 0.069	***p* = 0.007**	
Week 8	55.04 (2.2)	52.10 (2.6)	60.93 (2.3)				*p* = 0.37			

Bold type denotes $p < 0.05$. BMT, Body in Mind Training; FLX, fluoxetine; GAD-7, Generalized Anxiety Disorder 7-item scale; HAM-A, Hamilton Anxiety Rating Scale; PSWQ, Penn State Worry Questionnaire; QoL, Quality of Life and Psychoeducation; WHOQOL-BREF, WHO Quality of Life Scale.
[a] Adjusted for age, gender, education level, agoraphobia and major depression at baseline, baseline HAM-D, and each scale's score at baseline.

Forty-three participants did not attend the first session (8 in BMT, 9 in FLX, and 26 in QoL; Pearson's chi-squared = 16.087; df = 2; p < .001). Residual analysis revealed that more participants in the QoL group did not attend the first session, and there was no difference between the BMT and FLX groups. The participants participated in 5.67 (±2.5) sessions in the BMT and 4.96 (±2) in the QoL group. The mean dose of FLX at the end of the treatment was 32.64 mg (±11.7). Dropout reasons from those participants who attended the first session were: adverse situations of life, e.g., patient or family illness (8 in BMT, 1 in FLX, and 2 in QoL); loss of availability to attend treatment (9 in BMT, 1 in FLX, and 7 in QoL); adverse effects (1 in BMT, 5 in FLX, and 1 in QoL); lack of efficacy (3 in BMT, 1 in FLX, and 4 in QoL); loss of motivation (1 in BMT); and unknown reason (7 in BMT, 1 in FLX, and 6 in QoL). We reported only one severe adverse effect (hypomanic symptoms in FLX). See *Figure 1* for a CONSORT flow chart of randomization, dropouts, and missing items for each group.

Masking

The magnitude of discrepancy between the active group and the group that the blinded clinician evaluator attributed to the participant was 0.2 (kappa coefficient) indicating low agreement and a successful blinding.

Main findings

Primary outcomes

All three groups had improved at the end of treatment compared with baseline assessment considering HAM-A and PSWQ scores. We showed significant time-by-group interactions (p = .004) for the HAM-A scale. However, GEE contrasts revealed BMT was not superior to QoL (mean difference = -1.36; CI 95% -5.05 to 2.33; p = .47) and did not show non-inferiority compared with FLX according to the HAM-A rating scale (mean difference = 3.5; CI 95% -0.06 to 7.06; non-inferiority margin = -2.43; p = .054). See Table 2 for more details. *Figure 1S, Supplemental Material* depicts HAM-A scores and standard error (SE) for each group over the time period.

Considering the PSWQ, there was a significant time-by-group interaction (p = .004). We demonstrated that both QoL (mean difference = 3.54; CI 95% 0.16 to 6.92; p = .04) and FLX (mean difference = -7.72; CI 95% -10.89 to -4.56; non-inferiority margin = -2.09; p < .001) were superior to BMT in reducing worries assessed through the PSWQ (Table 2). See also *Figure 2S, Supplemental Material* for more details.

The analyses of the participants who completed the 8-week protocol (completers) showed similar results to those of the ITT analyses for HAM-A and PSWQ. For more details about completers analyses, see the *Supplemental Material*.

Considering the comparison between FLX and QoL groups, FLX was superior to QoL in improving symptoms according to the HAM-A score (mean difference = -4.86; CI 95% -8.4 to -1.32; p = .007) and PSWQ (mean difference = -4.18; CI 95% -7.53 to -0.84; p = .014). Table 3 shows the mean differences of score levels from baseline to endpoint of each intervention and the effect size of the differences compared with BMT.

Secondary outcomes

All three groups had improved at the end of the interventions compared with the baseline assessment and we detected significant time-by-group interaction according to GAD-7 (Table 2). GEE contrasts showed that BMT was not superior to QoL (mean difference = -0.35; CI 95% -3.54 to 2.84; p = .83), whereas FLX was superior to BMT (mean difference = -2.9; CI 95% -5.27 to -0.52; p = 0.017). Moreover, FLX was superior to the QoL group (mean difference = -3.25; CI 95% -6.03 to -0.47; p = .022). See *Figure 2S, Supplemental Material* for more details. We also did a sensitivity analysis with all randomized individuals despite attending or not the first session using the GAD-7. The results were the same according to the GEE analysis. See *Supplemental Material* for more details.

Additionally, all three groups had improved their quality of life at the end of treatment when compared with baseline. However, significant time-by-group interactions were detected. BMT was not superior (mean difference = 2.94; CI 95% -3.49 to 9.38; p = .37), but FLX was superior to QoL for improving quality of life (mean difference = 8.83; CI 95% 2.45 to 15.22; p = .007). BMT did not show non-inferiority compared with FLX (mean difference = 5.89; CI 95% -0.45 to 12.22; non-inferiority margin = 4.42; p = .069) (Table 2).

Analyses of the completers when considering the secondary outcomes showed the same results for GAD-7, but did not show time-by-group interaction when considering the WHOQOL assessment. See *Supplemental Material* and *Supplemental Figure 2* for more details.

There were no differences in response and remission rates between the groups. The response rate for BMT, FLX, and QoL was 40% (18/46), 50% (30/60), and 28.9% (11/38), respectively (p = .117), while the remission rate was 19.6% (9/46), 21.7% (13/60), and 10.5% (4/38), respectively (p = .358). Table 3 provides the mean differences of score levels from baseline to endpoint of each intervention and the effect size of the differences compared with BMT.

Discussion/Conclusion

Our results showed that, although patients from the three interventions improved after eight weeks, the BMT group was not superior to QoL (used as an active comparison group) and failed to show non-inferiority to FLX for reducing anxiety symptoms in GAD patients. Results were consistent across clinician- and patient-rated outcomes and BMT should not be considered effective for treating anxiety symptoms in GAD patients, which is at variance from our “a priori” hypothesis. The FLX group was superior to QoL on the HAM-A scale and in all other clinical assessments. Furthermore, FLX was superior to BMT when we measured worry through the PSWQ scale and when we measured anxiety symptoms through GAD-7.

Despite some similarities between GAD and major depressive disorder, we failed to replicate the superiority of MBIs compared with active controls in the treatment of acute depression episodes or in the prevention of relapses in this study with GAD patients (46,47). However, we should emphasize that these studies evaluated the efficacy of MBCT and not BMT in depression. Considering GAD, three previous randomized clinical trials (16,19,20) had investigated the efficacy of MBIs. In agreement with our study, all trials reported a significant reduction in anxiety severity with MBIs. However, inconsistent with our results, Asmaee Majid *et al*. (16) found that MBSR were better than an active comparison group in decreasing anxiety symptoms. Nevertheless, Hoge *et al*. (19) found that, although MBI reduced anxiety symptoms,

it was superior to the control group only in improving the Beck Anxiety Inventory (BAI) score, but not in decreasing the HAM-A score. Moreover, in agreement with our results, Wong *et al*. (20) did not find superiority of MBI in reducing anxiety assessed by BAI or PSWQ when compared with a psychoeducation group.

While previous studies used the MBSR (16,19) or the MBCT (17,20), our study was the first to evaluate the BMT protocol in GAD patients. BMT was developed based on the same meditation theory as MBSR or MBCT, and its five components (pause, intention, attention, self-understanding, and compassion) came all from the standard mindfulness definition of Kabat-Zinn (24). However, whereas MBSR uses a static posture to anchor attention, BMT provides an alternative way of practicing, using body movement as an anchor (22,24). Nevertheless, our study could not find the putative superiority of this protocol enhancement. The shorter number of sessions (16 h vs. 30 h) and the fact that BMT protocol does not include an all-day retreat, which according to a recent review (48), may moderate the effect of MBIs in improving mindfulness trace might account for our negative findings.

Additionally, despite studies investigating the important effect of MBIs in improving anxiety in healthy individuals (49), the lack of relative efficacy of BMT compared with QoL might be understood by considering some specific aspects of the protocol and anxiety symptoms. The BMT modality invites patients to be aware of bodily sensations and to accept their anxious symptoms, which can be challenging for GAD patients because of the presence of anxiety sensitivity and avoidant behaviors. Interestingly, the BMT group had almost twice as many agoraphobic and panic-disordered patients compared with the FLX group, which are disorders known to be associated with high anxiety sensitivity that can interfere with attention to the body, a core characteristic of BMT. Patients in the BMT group were also invited to learn, train, and develop an innovative perspective of self-care and emotional management, which can be more complex and require greater effort than using medication. These new abilities may need more than eight weeks to promote changes and improvement and we did not assess follow-up data.

Some limitations of our study should be noted. First, the dropout rates from BMT and QoL were higher than the FLX group, and our rates are higher as compared with other studies that evaluated MBIs to treat GAD, such as MBSR (6%) (19) and MBCT (10%) (20). Participants were included if they could attend the meetings, but our data suggested that the personal disposition toward attending weekly sessions might have decreased group adherence. However, all analyses considered the treatment of missing data to reduce biases. Second, we did not assess home practice adherence. Nevertheless, adherence to homework is part of

adherence to treatment as a whole. This may be a problem in all studies that evaluate psychotherapies that are more prone to assessing effectiveness than efficacy. Third, we did not have a follow-up measure so we could not assess participants over time and evaluate the longitudinal effects of psychological interventions or medication discontinuation concerning chronicity, relapses, or withdrawal syndromes (50). Fourth, given that BMT is a new treatment modality, an instrument for adherence was not available. Albeit, the therapist delivering BMT was trained by the therapist who elaborated the BMT protocol (21) and was supervised to assure adherence to the protocol. Finally, we reported only one severe side effect (hypomanic symptoms in one patient) but we had no data on mild or moderate side effects in the FLX group. However, it is important to highlight that fewer participants in the FLX group deteriorated during the study when compared with the BMT and QoL groups.

Our results may not be generalized to other MBIs. Furthermore, we should take into consideration some external validities when comparing psychotherapy with a control intervention (28). Despite carefully developing an active comparison group to control for common, unspecific, and placebo factors associated with psychotherapy efficacy and response, the lack of superiority of BMT compared with QoL in our study did not mean that BMT did not promote improvement. Each intervention can either lead to similar outcomes through different mechanisms (51) or can promote improvement through nonspecific psychotherapeutic factors such as therapeutic alliance, empathy, goal consensus and expectancy, and also can be influenced by unspecific group factors such as hope, socialization, interpersonal learning, and universality. However, the use of an active control group is an important design since the comparison with waiting list, for example, produces an effect known as nocebo (49). Previous meta-analyses have reported different results when MBIs were compared with active controls or with evidence-based treatments (such as CBT) (52,53). Also, it is difficult to evaluate the results of psychotherapy intervention trials because the research environment usually differs from routine practices (28). Therefore, results from the comparison of BMT with FLX and QoL should be interpreted carefully. Finally, intervention side effects despite quitting the study were not measured, which is a recurrent problem in psychotherapy studies (54).

However, our study has important strengths. First, this is the first study to assess BMT protocol in patients with GAD. Second, it is also the first study comparing MBI to medication in GAD patients, which could contribute important information to real-life clinical decisions. Finally, we have methodological strengths such as adequate sample size and an active comparison group with active ingredients of psychoeducation, therapeutic alliance, social support, attention from therapists, and the practice of healthy habits that impact anxiety.

In summary, this is a negative study. Even though the three groups improved after the intervention, contrary to our hypothesis, BMT (a mindfulness-based intervention) was not superior to QoL (an active comparison group) and was inferior to FLX in improving anxiety symptoms in GAD patients. BMT did not show benefit in treating GAD patients in its current format.

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Statement of Ethics

Subjects have given their written informed consent and that the study protocol was approved by the Hospital de Clínicas de Porto Alegre's committee on human research.

Conflict of Interest Statement MAC, FG, NKF, JKS, SGA, GAS, GGM declare no conflicts of interest. GGM receives a senior research scholarship from Brazilian government agency (number 306249/2017-0); TT is a cofounder of Iniciativa Mindfulness in Brazil.

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Author Contributions

MAC: helped on the concept and the design of the work; helped on the acquisition of the data; developed the analysis and interpretation of data; and drafting the work.

FG: helped on the concept and the design of the work; helped on the acquisition of the data; helped on the interpretation of data; and revised the work.

TT: helped on the concept and the design of the work; helped on the acquisition of the data; helped on the interpretation of data; and revised the work.

NKF: helped on the concept and the design of the work; helped on the acquisition of the data; helped on the interpretation of data; and revised the work.

JKS: helped on the acquisition of the data; helped on the interpretation of data; and revised the work.

SGA: helped on the acquisition of the data; helped on the interpretation of data; and revised the work.

GAS: helped on the concept and the design of the work; helped in the analysis and interpretation of data; revised the work critically.

GGM: helped on the concept and the design of the work; helped in the analysis and interpretation of data; revised the work critically.

REFERENCES

1. Kessler RC, Angermeyer M, Anthony JC, DE Graaf R, Demyttenaere K, Gasquet I, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry Off J World Psychiatr Assoc WPA. 2007 Oct;6(3):168–76.

2. Comer JS, Blanco C, Hasin DS, Liu S-M, Grant BF, Turner JB, et al. Health-related quality of life across the anxiety disorders: results from the national epidemiologic survey on alcohol and related conditions (NESARC). J Clin Psychiatry. 2011 Jan;72(1):43–50.

3. Ruscio AM, Hallion LS, Lim CCW, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, et al. Cross-sectional Comparison of the Epidemiology of DSM-5 Generalized Anxiety Disorder Across the Globe. JAMA Psychiatry. 2017 01;74(5):465–75.

4. Revicki DA, Travers K, Wyrwich KW, Svedsäter H, Locklear J, Mattera MS, et al. Humanistic and economic burden of generalized anxiety disorder in North America and Europe. J Affect Disord. 2012 Oct;140(2):103–12.

5. Bandelow B, Boerner J R, Kasper S, Linden M, Wittchen H-U, Möller H-J. The diagnosis and treatment of generalized anxiety disorder. Dtsch Arzteblatt Int. 2013 Apr;110(17):300–9; quiz 310.

6. Yonkers KA, Dyck IR, Warshaw M, Keller MB. Factors predicting the clinical course of generalised anxiety disorder. Br J Psychiatry J Ment Sci. 2000 Jun;176:544–9.

7. Mavranezouli I, Meader N, Cape J, Kendall T. The cost effectiveness of pharmacological treatments for generalized anxiety disorder. PharmacoEconomics. 2013 Apr;31(4):317–33.

8. Goldberg SB, Tucker RP, Greene PA, Davidson RJ, Wampold BE, Kearney DJ, et al. Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. Clin Psychol Rev. 2018;59:52–60.

9. 1 Guidance | Depression in adults: recognition and management | Guidance | NICE [Internet]. [cited 2019 Aug 19]. Available from: https://www.nice.org.uk/guidance/cg90/chapter/1-Guidance

10. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol. 2010 Apr;78(2):169–83.

11. Strauss C, Cavanagh K, Oliver A, Pettman D. Mindfulness-based interventions for people diagnosed with a current episode of an anxiety or depressive disorder: a meta-analysis of randomised controlled trials. PloS One. 2014;9(4):e96110.

12. Vøllestad J, Nielsen MB, Nielsen GH. Mindfulness- and acceptance-based interventions for anxiety disorders: a systematic review and meta-analysis. Br J Clin Psychol. 2012 Sep;51(3):239–60.

13. de Abreu Costa M, D'Alò de Oliveira GS, Tatton-Ramos T, Manfro GG, Salum GA. Anxiety and Stress-Related Disorders and Mindfulness-Based Interventions: a Systematic Review and Multilevel Meta-analysis and Meta-Regression of Multiple Outcomes. Mindfulness [Internet]. 2018 Nov 15 [cited 2019 Feb 9]; Available from: https://doi.org/10.1007/s12671-018-1058-1

14. Evans S, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. J Anxiety Disord. 2008 May;22(4):716–21.

15. Kabat-Zinn J, Massion AO, Kristeller J, Peterson LG, Fletcher KE, Pbert L, et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. Am J Psychiatry. 1992 Jul;149(7):936–43.

16. Asmaee Majid S, Seghatoleslam T, Homan H, Akhvast A, Habil H. Effect of mindfulness based stress management on reduction of generalized anxiety disorder. Iran J Public Health. 2012;41(10):24–8.

17. Kim YW, Lee S-H, Choi TK, Suh SY, Kim B, Kim CM, et al. Effectiveness of mindfulness-based cognitive therapy as an adjuvant to pharmacotherapy in patients with panic disorder or generalized anxiety disorder. Depress Anxiety. 2009;26(7):601–6.

18. Boettcher J, Aström V, Påhlsson D, Schenström O, Andersson G, Carlbring P. Internet-based mindfulness treatment for anxiety disorders: a randomized controlled trial. Behav Ther. 2014 Mar;45(2):241–53.

19. Hoge EA, Bui E, Marques L, Metcalf CA, Morris LK, Robinaugh DJ, et al. Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: effects on anxiety and stress reactivity. J Clin Psychiatry. 2013 Aug;74(8):786–92.

20. Wong SYS, Yip BHK, Mak WWS, Mercer S, Cheung EYL, Ling CYM, et al. Mindfulness-based cognitive therapy v. group psychoeducation for people with generalised anxiety disorder: randomised controlled trial. Br J Psychiatry J. 2016;209(1):68–75.

21. Russell T. Body in mind training: mindful movement for severe and enduring mental illness. Br J Wellbeing. 2011 Apr 1;2(4):13–6.

22. Russell T. Mindfulness in Motion: Unlock the Secrets of Mindfulness in Motion. Place of publication not identified: Watkins Publishing; 2015. 144 p.

23. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092–7.

24. Russell TA, Arcuri SM. A Neurophysiological and Neuropsychological Consideration of Mindful Movement: Clinical and Research Implications. Front Hum Neurosci. 2015;9:282.

25. Russell T.A., Tatton-Ramons T. Body in mind training: mindful movement for the clinical settin. Neuro Disabil Psychother. 2.

26. Wampold BE, Imel ZE. The great psychotherapy debate: The evidence for what makes psychotherapy work, 2nd ed. New York, NY, US: Routledge/Taylor & Francis Group; 2015. x, 323 p. (The great psychotherapy debate: The evidence for what makes psychotherapy work, 2nd ed).

27. Guidi J, Brakemeier E-L, Bockting CLH, Cosci F, Cuijpers P, Jarrett RB, et al. Methodological Recommendations for Trials of Psychological Interventions. Psychother Psychosom. 2018;87(5):276–84.

28. Zipfel S, Junne F, Giel KE. Measuring Success in Psychotherapy Trials: The Challenge of Choosing the Adequate Control Condition. Psychother Psychosom. 2020 May 6;1–5.

29. Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. BMJ. 2011 Mar 11;342:d1199.

30. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet Lond Engl. 2019 23;393(10173):768–77.

31. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.

32. Amorim P. Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. Braz J Psychiatry. 2000 Sep;22(3):106–15.

33. American Psychiatric Association, American Psychiatric Association, editors. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C: American Psychiatric Association; 2013. 947 p.

34. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50–5.

35. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behav Res Ther. 1990;28(6):487–95.

36. Castillo C, Macrini L, Cheniaux E, Landeira-Fernandez J. Psychometric properties and latent structure of the Portuguese version of the Penn State Worry Questionnaire. Span J Psychol. 2010 May;13(1):431–43.

37. Busner J, Targum SD. The Clinical Global Impressions Scale. Psychiatry Edgmont. 2007 Jul;4(7):28–37.

38. Moreno AL, DeSousa DA, Souza AMFLP de, Manfro GG, Salum GA, Koller SH, et al. Factor structure, reliability, and item parameters of the brazilian-portuguese version of the GAD-7 questionnaire. Temas Em Psicol. 2016 Mar;24(1):367–76.

39. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967 Dec;6(4):278–96.

40. Carrozzino D, Patierno C, Fava GA, Guidi J. The Hamilton Rating Scales for Depression: A Critical Review of Clinimetric Properties of Different Versions. Psychother Psychosom. 2020;89(3):133–50.

41. Carneiro AM, Fernandes F, Moreno RA. Hamilton depression rating scale and montgomery–asberg depression rating scale in depressed and bipolar I patients: psychometric properties in a Brazilian sample. Health Qual Life Outcomes [Internet]. 2015 Apr 2 [cited 2019 Feb 7];13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4391145/

42. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. [Application of the Portuguese version of the abbreviated instrument of quality life WHOQOL-bref]. Rev Saude Publica. 2000 Apr;34(2):178–83.

43. Allgulander C, Hartford J, Russell J, Ball S, Erickson J, Raskin J, et al. Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. Curr Med Res Opin. 2007 Jun;23(6):1245–52.

44. Huibers MJH, Cohen ZD, Lemmens LHJM, Arntz A, Peeters FPML, Cuijpers P, et al. Predicting Optimal Outcomes in Cognitive Therapy or Interpersonal Psychotherapy for Depressed Individuals Using the Personalized Advantage Index Approach. PLoS ONE [Internet]. 2015 Nov 10 [cited 2020 Jul 28];10(11). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4640504/

45. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. N Engl J Med. 2017 29;376(26):2523–33.

46. Kuyken W, Warren FC, Taylor RS, Whalley B, Crane C, Bondolfi G, et al. Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials. JAMA Psychiatry. 2016 Jun 1;73(6):565–74.

47. Parikh SV, Quilty LC, Ravitz P, Rosenbluth M, Pavlova B, Grigoriadis S, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 2. Psychological Treatments. Can J Psychiatry Rev Can Psychiatr. 2016;61(9):524–39.

48. Visted E, Vøllestad J, Nielsen MB, Nielsen GH. The Impact of Group-Based Mindfulness Training on Self-Reported Mindfulness: a Systematic Review and Meta-analysis. Mindfulness. 2015 Jun;6(3):501–22.

49. Khoury B, Sharma M, Rush SE, Fournier C. Mindfulness-based stress reduction for healthy individuals: A meta-analysis. J Psychosom Res. 2015 Jun;78(6):519–28.

50. Cosci F, Chouinard G. Acute and Persistent Withdrawal Syndromes Following Discontinuation of Psychotropic Medications. Psychother Psychosom. 2020;89(5):283–306.

51. Rosenkranz MA, Dunne JD, Davidson RJ. The next generation of mindfulness-based intervention research: what have we learned and where are we headed? Curr Opin Psychol. 2019 Aug;28:179–83.

52. de Abreu Costa M, D'Alò de Oliveira GS, Tatton-Ramos T, Manfro GG, Salum GA. Anxiety and Stress-Related Disorders and Mindfulness-Based Interventions: a Systematic Review and Multilevel Meta-analysis and Meta-Regression of Multiple Outcomes. Mindfulness. 2019 Jun;10(6):996–1005.

53. Goldberg SB, Tucker RP, Greene PA, Davidson RJ, Wampold BE, Kearney DJ, et al. Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. Clin Psychol Rev. 2018 Feb;59:52–60.

54. Fava GA, Rafanelli C. Iatrogenic Factors in Psychopathology. Psychother Psychosom. 2019;88(3):129–40.